UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Università degli studi di Padova

Dipartimento di Psicologia Generale

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE PSICOLOGICHE

CICLO XXX

Elaborato Finale:

On the effects of transcranial alternating stimulation (tACS) on neuronal dynamics and cognition.

Tesi redatta con il contributo finanziario della fondazione CARIPARO

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Abbreviations

ACC anterior cingulate cortex

AD Alzheimer's disease

APs amyloid plaques

A-tDCS anodal tDCS

BG basal ganglia

CR cognitive Reserve

CSP cortical silent period

cTBS continuous theta burst stimulation

C-tDCS cathodal tDCS

DBS deep brain stimulation

DLPFC dorsolateral prefrontal cortex

DM dorso medial thalamic region

EEG electroencephalography

EMG electromyography

ERD event related desynchronization

ERS event related synchronization

FDI first dorsal interosseous muscle

FEF frontal eye field

fMRI functional magnetic resonance imaging

GABA ϒ-aminobutyric acid

GM gray matter

GP globus pallidus

GPe globus pallidus external part

GPi globus pallidus internal part

Hz Herz

IAF individual alpha frequency

ICF intra cortical facilitation

IFC inferior frontal cortex

ISI inter stimulus interval

iTBS intermittent theta burst stimulation

kΩ kilo ohms

LFP local field potentials

LICI Long interval cortical inhibition

L-PPC left posterior parietal cortex

LRP lateralized readiness potential

LTD long term depression

LTP long term potentiation

L-TPC left temporal parietal cortex

M1 primary motor cortex

mA milliampere

MEG magnetoenchephalografy

MEP motor evoked potential

mNCD mild neurocognitive disorder

MRI magnetic resonance imaging

MRS magnetic resonance spectroscopy

ms milliseconds

MSN medium spiny neurons

MT motor threshold

NAcc nucleus accumbens

NCE negative compatibility effect

NFTs neurofibrillary tangles

NIBS non invasive brain stimulation

NMDA N-methyl-D- aspartate

OFC orbito frontal cortex

PCE positive compatibility effect

PD Parkinson's Disease

PSD power spectral density

pTMS paired pulse TMS

QoL quality of life

R-PPC right posterior parietal cortex

RT reaction times

rTMS repetitive TMS

R-TPC right temporal parietal cortex

SAI Short Afferent Inhibition

SEF supplementary eye field

SICI Short-interval cortical inhibition

SMA supplementary motor area

SMC supplementary motor complex

SN substantia nigra

SNc substantia nigra pars compacta

SNr substantia nigra pars reticulata

SR stochastic resonance

STDP spike Timing Dependent Plasticity

sTMS single pulse TMS

STN subthalamic nucleus

tACS transcranial alternating current stimulation

tCS transcranial current stimulation

tDCS transcranial direct current stimulation

TMS transcranial magnetic stimulation

VA ventral anterior thalamic region

VL ventral lateral thalamic regions

VTA ventral tegmental area

WM white matter

Acknowledgements

To my late mother Cinzia Balos: for your love and your eternal encouragement. I miss you and I would never ever forget our interesting, long-lasting and profound conversations on the most disparate subjects, spreading between art, science, philosophy and spirituality. I became what I am thanks to you. I miss you. Many Thanks!

To my late grandfather Aldo Balos your teachings, your values and your incessant curiosity, have helped me become what I am. Thanks nonno!

I am grateful to my sibling Ginevra and Simon Pietro, who have morally and emotionally supported me in my life. I love you so much.

A special thanks to my encouraging and always enthusiastic grandma nonna Carmen, I will never forget her words after the discussion of my first degree: -Davide I did not understand anything of what you said but you were very good, the number one!!! nonno Aldo said: She was forever keen to know what I was doing although it is likely that she has never grasped what it was all about! Thanks nonna!

I am also grateful to my other family members who have supported me along the way.

I would like to express my sincere gratitude to my advisor Prof. Patrizia Bisiacchi for the continuous support of my Ph.D study and related research, for her patience, and immense enthusiasm for research. I appreciate all your contributions of time and ideas to make my Ph.D. experience a productive and stimulating one. Your guidance helped me before and during my Phd and I could not have imagined having a better advisor and mentor for my Ph.D study.

I would like also thank my Co-supervisors in London Prof. John Rothwell and Prof. Marjan Jahanshahi, for their insightful comments and encouragement. Of fundamental importance were our discussions regarding paradigms, results, methodology and experimental innovation that shaped my research profile and my skills.It has been an amazing experience to work with you. I would like also thank the reviewers of my doctoral thesis for their valuable comments and corrections.

For my wonderful time in London I would like to thank all the members of the Functional Neurosurgery Unit at the National Hospital of Neurology and Neurosurgery at Queen Square, Marwan Hariz, Patricia Limousin, Tom Foltynie, Vish Dayal, Dylan Athauda, Akram Harith, Tim Grover and Linda Taib, it was great to be part of your team. A special thank and my heartfelt appreciation goes to Sasha Ondobaka, a friend and a mentor. For having taught me the art of smothification of the body and the soul. I will never forget the time spent together at Keeling House in London.

I thank my labmates and collaborators Gianvito Laera and Anahita Goljahani for the stimulating discussions, for the sleepless nights we were working together before deadlines, and for all the fun we have had in the last four years. For my wonderful time in Padova I would like to thank my fellow doctoral students Rocco Mennella e Davide

Stramaccia for their feedback, cooperation and of course friendship. I am sure that without our profitable scientific conversations accompanied by a guitar and a glass of tequila this doctorate would not have been the same. I am also grateful to the following friends and colleagues that I met at the University of Padova Elisabetta, Nicola, Silvia, Diana, Sara, Eleonora, Michele, Tommaso, Sonia, Luca, Francesco, Elias, Giorgia, Giorgio, Vincenza, Waldir and all members of the football team of the DPG and the secretariat of the DPG.I also would like to thank my friend Luca Serra, you have been a constant resource of ideas and I hope that one day you will succeed in realizing them.

I also place on record, my sense of gratitude to one and all who directly or indirectly, have lent their helping hand in this venture.

Davide Balos Cappon
Boston
January 2018

"*riequilibrare gli equilibri*"

Cinzia Balos Aiznic Solab

"None are more hopelessly enslaved than those who falsely believe they are free."

Johann Wolfgang von Goethe

1 INTRODUCTION

1.1 Introduction and aims of the thesis

A few minutes at a busy square in London allow one to appreciate the wide array of actions that humans are capable of expressing— walking, reading a book, tapping touch screen of smartphone, eating, shaking hands and crossing the street.

Response inhibition is an essential mechanism of action control and is one of the most studied processes. For example, crossing the street when a fast motorcycle is approaching might necessitate inhibition of stepping forward to avoid being hurt. This ability to quickly suppress a response in a dynamic environment has traditionally been associated with conscious control. Crucially, recent experimental evidence has challenged the view that inhibitory control is restricted to conditions where stimuli are accessible to conscious awareness. Such an unconscious and automatic activation of the motor response system does not necessarily require stimuli to be consciously perceived and is deemed essential to act in a constantly changing environment. This has been interpreted as a basic motor process allowing preparatory mechanisms to automatically suppress an activated movement without the need of conscious cognitive processes. Thus, while there may be differences between automatic and voluntary processes, they might not have entirely distinct neural representations. Indeed, automatic control appears to rely on the cortico-basal ganglia network that has been associated with voluntary control. Contemporary research has shown that an up-regulation of neural beta oscillations in the cortico-basal ganglia dynamics can be functionally relevant for inhibition of movement. Consequently, beta oscillations have been proposed as an essential mechanism that allow the motor network to communicate in a dynamic and flexible manner. Present research has demonstrated that it is possible to interact with the neuronal activity by non invasive brain stimulation (NIBS) techniques such as transcranial Direct Current Stimulation (tDCS),

transcranial Alternating Current Stimulation (tACS). Specifically, tACS allows delivery of alternating current at different frequencies and it has been used to manipulate ongoing brain oscillations in a controllable way. This concept is still in the very early stages of research, and much needs to be done in order to fully grasp the underlying mechanisms. Building upon these discoveries, the research presented in this thesis aimed to demonstrate a causal role of beta frequency oscillations on unconscious and automatic inhibition adopting tACS over the primary motor cortex and supplementary motor area. Furthermore combining tACS with TMS and EEG allowed me to characterise the underlying basic mechanisms of its action on corticospinal excitability and neuronal dynamics. Overall, this work contributes to our understanding of the human motor system while offering new insights into the combined approach of tACS and EEG in the characterization of a causal role of neuronal oscillatory dynamics on behaviour.

1.2 Summary

The second chapter of the thesis provides the theoretical background related to important themes that will surface throughout the thesis and is composed of three paragraphs. The first paragraph briefly defines the theoretical framework to study the control of action in a dynamic environment. I discuss recent evidence that challenged the view that inhibitory control is restricted to conditions where stimuli are accessible to conscious awareness. In this framework I propose that unconscious automatic inhibition might be an essential process in all behaviours. Then I provide a brief summary of the experimental paradigms adopted in the laboratory to measure rapid control of action and examine in detail the masked prime task used in this thesis. The second paragraph provides some basic notions of the neuronal anatomy underlying automatic action control. In particular, it describes areas of the basal ganglia (BG) and the cortex that have been implicated in the automatic control of action. The third paragraph provides a brief summary of the literature relating to

human beta oscillations. Different accounts of the functional role of beta oscillations will be discussed. Some accounts focused on the role of beta in the sensorimotor system as an 'idling system' (Pfurtscheller & Lopes da Silva, 1999); others reviewed evidence from recent studies of cognitive processing of the motor system and on the pathophysiology of movement disorders suggesting that beta-band activity relates to maintenance of the current sensorimotor or cognitive states (Engel & Fries, 2010). Finally, recent work on endogenous information processing in working memory and decision making suggests a role for beta oscillations in endogenous content (re)activation.

The third chapter aims to provide some basic notions of neurophysiology describing basic concepts of neuronal communication that is a prerequisite for understanding the mechanisms by which transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) affects with brain activity. I then describe the recent evidence on the ability of tACS to modulate perceptual and cognitive processes in a frequency specific manner and why this possibility to drive intrinsic brain oscillations through the injection of sinusoidal currents provides an advantage compared to tDCS and rTMS.

The aims of the current thesis are two-fold: the first is to bridge lines of research on the automatic mechanisms of motor inhibition and on the role of beta oscillation in the sensorimotor system. To investigate the hypothesis that beta oscillations are functionally relevant I have exploited the ability of transcranial alternating stimulation to modulate perceptual and cognitive processes in a frequency specific manner. The second aim was to investigate the neurophysiological mechanisms underlying the effects of tACS applied at physiologically relevant beta (20 Hz) and alpha (10 Hz) frequencies on motor cortical neuronal dynamics. Specifically, I adopted a combined approach tACS-TMS and tACS-EEG to characterize respectively the modulation of corticospinal excitability and the interactions with the neuronal dynamics.

In the chapters that follow (4-7), I present studies that I conducted during my PhD. The first study (Chapter 4) is a review of literature highlighting the limits, the methodological issues and technical aspects of the tDCS in modulating cognition, namely -- electrode position and dimension; current intensity; duration of protocol, inclusion of appropriate assessment tools for cognition, optimal timing for administration of tDCS for cognitive rehabilitation. This review has been crucial to highlight the limits of direct current stimulation. Experimental evidence showed the ability of tACS to modulate perception and cognitive processes in a frequency specific manner in particular in the motor cortex. I took advantage of the emergence of this technique to investigate whether automatic inhibition processes are influenced by tACS in a frequency specific manner. Indeed, recent evidence focused on the role of beta in the sensorimotor system, in particular during motor inhibition (see Chapter 2). Therefore, the second study (Chapter 5) was aimed to investigate the functional role of beta frequency in automatic motor processes using tACS to interact non-invasively with the ongoing task-related oscillatory activity. Stimulation was delivered at alpha (10 Hz) and beta (20 Hz) frequency over the supplementary motor area and the primary motor cortex (SMA-M1) connections, which are part of the BG-cortical motor loop, during execution of the subliminal masked prime task. I found that 20 Hz tACS increased the duration of automatic inhibition whereas the duration was decreased after 10 Hz tACS. The findings of this experiment highlighted a distinct frequency dependent effect of tACS on automatic motor behavioural performance. Note that this is consistent with the idea that 20 Hz tACS enhances beta activity in the motor network as previously proposed by other groups for explaining slowed movement after of 20 Hz tACS (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Pogosyan, Gaynor, Eusebio, & Brown, 2009). Consistent with these results, the second study was conducted by a combined TMS-tACS approach to investigate the hypothesis of frequency-specific

neuromodulatory effects of tACS on motor corticospinal excitability. Again, I found that 10 Hz and 20 Hz tACS have different effects on the excitability of the primary motor cortex. 20 Hz tACS led to a significant decrease of the amplitude of motor evoked potentials (MEPs) evoked by single pulse TMS while I observed no changes after 10Hz. Together, the findings in the second and the third study (Chapters 5and 6) suggest that 20 Hz tACS application on the motor cortex may interact with neuronal dynamics but cannot conclusively speak to this possibility. In an effort to elucidate the efficacy of tACS in modulating specific oscillatory network activity, in the fourth study (Chapter 7) I employed a combined EEG-tACS approach to measure time-varying changes in alpha and beta bands following tACS. I adopted an EEG-tACS co-registration methodology which allowed to record EEG right after stimulation from a large array of EEG sensors (i.e., 45) to investigate the neuromodulatory effects of tACS on motor neuronal oscillatory dynamics. Crucially, I found beta band oscillations as being significantly amplified by the application of 20Hz tACS over motor cortical areas. To my knowledge, this is the first study to report a 20 Hz tACS-induced modulation of sensorimotor beta rhythm. The findings from these studies provide insight into the understanding and the practical application of transcranial alternating current stimulation in modulating motor neuronal dynamics.

1.3 Riassunto

Alcuni minuti in una piazza affollata di Londra permettono di apprezzare l'ampia gamma di azioni che gli esseri umani sono capaci di esprimere— camminare, leggere un libro, toccare lo schermo dello smartphone, mangiare, stringere la mano e attraversare la strada.

L'inibizione della risposta è un meccanismo essenziale del controllo motorio dell'azione e rappresenta uno dei processi più studiati. Ad esempio, attraversare la strada quando inavvertitamente si avvicina una motocicletta a grande velocità potrebbe richiedere

l'inibizione di mettere i piedi giù per evitare di essere feriti. Questa capacità di sopprimere rapidamente una risposta in un ambiente dinamico è stata tradizionalmente associata al controllo cosciente. In modo cruciale, recenti prove sperimentali hanno sfidato la concezione che il controllo inibitorio è limitato alle condizioni in cui gli stimoli sono accessibili alla consapevolezza cosciente. Tale attivazione inconscia e automatica del sistema motorio non necessariamente richiede che gli stimoli siano consapevolmente percepiti e si ritiene essenziale per agire in un ambiente in costante evoluzione. Questa attivazione è stata interpretata come un processo motorio basale che permette a meccanismi preparatori di sopprimere automaticamente un movimento attivato senza la necessità di processi cognitivi coscienti. Così, sebbene ci siano delle differenze tra i processi automatici e quelli volontari, tali processi potrebbero non avere rappresentazioni neurali completamente distinte. Infatti, il controllo motorio automatico sembra avere come substrato neurale il circuito corticale-ganglio basale che è stato associato al controllo motorio volontario. La ricerca contemporanea ha inoltre dimostrato che l'incremento delle oscillazioni beta nelle dinamiche del sistema corticale-ganglio basale può essere funzionalmente rilevante per l'inibizione del movimento. Di conseguenza, le oscillazioni beta sono state proposte come un meccanismo essenziale che consente al network motorio di comunicare in modo dinamico e flessibile. Nel frattempo, la ricerca attuale ha dimostrato che è possibile interagire con l'attività neuronale mediante tecniche di stimolazione cerebrale non invasiva (NIBS) come la stimolazione transcranica a corrente diretta (tDCS), la stimolazione transcranica a corrente alternata (tACS). In particolare, tACS consente la diffusione di corrente alternata a diverse frequenze ed è stata utilizzata per manipolare le oscillazioni cerebrali in modo controllabile. Comunque, questo concetto è ancora nelle fasi iniziali della ricerca e molto deve essere fatto per comprendere appieno i meccanismi sottostanti. Basandosi su queste scoperte, la ricerca presentata in questa tesi ha

lo scopo di dimostrare un ruolo causale delle oscillazioni neurali beta sull' inibizione inconscia e automatica, adottando la tACS sulla corteccia motoria primaria e l'area motoria supplementare. Inoltre, la combinazione di tACS con TMS e EEG mi ha permesso di caratterizzare i meccanismi di base della sua azione attraverso la misurazione dell'eccitabilità corticospinale e delle dinamiche oscillatorie neuronali. Nel complesso, questo lavoro contribuisce alla nostra comprensione del sistema motorio umano, offrendo al tempo stesso nuove conoscenze sull'approccio combinato di tACS e EEG nella caratterizzazione di un ruolo causale delle dinamiche oscillatorie neuronali sul comportamento. Il secondo capitolo della tesi fornisce il background teorico relativo a temi importanti che si sviscerano in tutta la tesi ed è composto da tre paragrafi. Il primo paragrafo, definisce brevemente il quadro teorico per studiare il controllo dell'azione in un ambiente dinamico. Discuto le recenti evidenze che hanno contestato la concezione che il controllo inibitorio è limitato alle condizioni in cui gli stimoli sono accessibili alla coscienza consapevole. In questo quadro propongo che l'inibizione automatica inconscia possa essere un processo essenziale in tutti i comportamenti. Poi fornisco un breve riassunto dei paradigmi sperimentali adottati in laboratorio per misurare il controllo rapido dell'azione ed esamino in dettaglio il paradigma utilizzato in questa tesi. Il secondo paragrafo fornisce alcune nozioni di base sull'anatomia neuronale sottostante il controllo automatico dell'azione. In particolare, descrive aree dei gangli della base e della corteccia cerebrale che sono state implicate nel controllo automatico dell'azione. Il terzo paragrafo fornisce un breve riassunto della letteratura relativa alle oscillazioni neurali funzionali al sistema motorio. Saranno discussi diversi contributi sul ruolo funzionale delle oscillazioni beta. Alcuni si sono concentrati sul ruolo delle oscillazioni beta nel sistema motorio come un 'idling system' (Pfurtscheller & Lopes da Silva, 1999); altri hanno esaminato le prove provenienti da recenti studi di elaborazione cognitiva del sistema motorio e sulla

fisiopatologia dei disturbi del movimento che suggeriscono che l'attività delle oscillazioni beta ha un ruolo funzionale al mantenimento degli stati cognitivi in corso (Engel & Fries, 2010). Infine, i recenti lavori sull'elaborazione dell'informazione nella memoria di lavoro e nel processo decisionale suggeriscono un ruolo per le oscillazioni beta nella riattivazione contestuale endogena (Spitzer & Haegens, 2017).

Il terzo capitolo fornisce una nozione di base della neurofisiologia e descrive i concetti fondamentali della comunicazione neuronale, che è un prerequisito per comprendere i meccanismi con cui la stimolazione transcranica magnetica (TMS) e la stimolazione transcranica a corrente alternata (tACS) influenzano l'attività cerebrale. Quindi descrivo le recenti evidenze sulla capacità della tACS di modulare i processi percettivi e cognitivi in modo frequenza specifico e perché questa possibilità di guidare oscillazioni intrinseche cerebrali attraverso l'iniezione di correnti sinusoidali offre un vantaggio rispetto alle tDCS e rTMS.

Gli obiettivi della tesi sono principalmente due: il primo è quello di collegare linee di ricerca sui meccanismi automatici di inibizione motoria al ruolo delle oscillazioni beta nel sistema neuronale motorio. Per esaminare questa ipotesi, ho sfruttato la capacità della stimolazione alternata transcranica di modulare i processi percettivi e cognitivi in modo frequenza specifico. Il secondo obiettivo è studiare i meccanismi neurofisiologici sottostanti agli effetti della tACS applicata alle frequenze fisiologiche beta (20 Hz) e alfa (10 Hz) sulle aree cerebrali motorie. In particolare, ho adottato l'approccio combinato tACS-TMS e tACS-EEG per caratterizzare rispettivamente la modulazione dell'eccitabilità corticospinale e le interazioni con la dinamiche neuronali.

Nei capitoli che seguono (4-7), presento gli studi che ho condotto durante il mio dottorato. Il primo studio (capitolo 4) è una revisione della letteratura che evidenzia i limiti, le

problematiche metodologiche e gli aspetti tecnici della tDCS nella modulazione dei processi cognitivi (posizione e dimensione dell'elettrodo, intensità, durata del protocollo, inclusione di strumenti di valutazione appropriati per la cognizione, tempi ottimali per la somministrazione di tDCS nella riabilitazione cognitiva). Questa rassegna è stata cruciale per evidenziare i limiti della stimolazione a corrente diretta. Nel frattempo, un crescente numero di prove sperimentali hanno dimostrato la capacità della tACS di modulare la percezione e i processi cognitivi in modo frequenza specifico, in particolare nella corteccia motoria. Dunque, ho approfittato dell'emergere di questa tecnica per indagare se i processi di inibizione automatica sono influenzati dalla tACS. Precisamente, le evidenze recenti hanno riguardato il ruolo della oscillazioni beta nel sistema motorio, in particolare durante l'inibizione motoria (vedi capitolo 2). Pertanto, il secondo studio (capitolo 5) ha lo scopo di indagare il ruolo funzionale della frequenza beta nei processi automatici motori utilizzando tACS per interagire in modo non invasivo con l'attività oscillatoria endogena cerebrale. La stimolazione è stata effettuata con frequenze alfa (10 Hz) e beta (20 Hz) sull'area motoria primaria e le connessioni con l'area supplementare motoria (SMA-M1), che fanno parte del circuito corticale-gangli della base, durante l'esecuzione di un compito di priming visuo-motorio. Ho scoperto che la somministrazione della tACS a 20 Hz ha aumentato la durata dell'inibizione automatica, mentre la durata dell'inibizione è stata ridotta dalla tACS a 10 Hz. I risultati di questo esperimento hanno messo in evidenza un diverso effetto della tACS, dipendente dalla frequenza, sulle prestazioni comportamentali che riflettono i processi motori automatici. Si noti che questo è coerente con l'idea che 20 Hz tACS aumenta l'attività delle oscillazioni beta nel network motorio come precedentemente proposto da altri gruppi per spiegare il movimento rallentato dopo l'applicazione di 20 Hz tACS (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Pogosyan , Gaynor, Eusebio, & Brown, 2009). Coerentemente con questi risultati, il secondo studio è stato condotto con un

approccio combinato TMS-tACS per indagare l'ipotesi di effetti neuromodulatori frequenza specifici della tACS sull'eccitabilità del tratto corticospinale. Ancora una volta, ho scoperto che 10 Hz e 20 Hz tACS hanno effetti diversi sull'eccitabilità della corteccia motoria primaria. 20 Hz tACS ha portato ad una significativa diminuzione dell'ampiezza dei potenziali evocati motori (MEP) evocati dalla TMS mentre non ho osservato cambiamenti significativi con 10Hz tACS. Insieme, i risultati del secondo e del terzo studio (capitoli 5 e 6) suggeriscono che l'applicazione della tACS a 20 Hz sulla corteccia motoria può interagire con le dinamiche neuronali, ma non può parlare definitivamente di questa possibilità. Nel tentativo di chiarire l'efficacia della tACS nella modulazione delle dinamiche oscillatorie specifiche, nel quarto studio (Capitolo 7) ho impiegato un approccio combinato EEG-tACS per misurare i cambiamenti nelle bande elettroencefalografiche alfa e beta. Per indagare gli effetti neuromodulatori della tACS sulle dinamiche oscillatorie ho adottato una metodologia di co-registrazione EEG-tACS che mi ha permesso di registrare EEG subito dopo la stimolazione da una vasta gamma di sensori EEG (i.e. 45). In modo cruciale, ho dimostrato che le oscillazioni nella banda beta sono significativamente amplificate dall'applicazione della tACS a 20Hz sulle aree corticali motorie. Secondo la nostra conoscenza, questo è il primo studio che dimostra una modulazione delle oscillazioni beta indotta da 20 Hz tACS sulle aree motorie. Concludendo, i risultati di questi studi consentono di comprendere l'applicazione pratica della stimolazione transcranica a corrente alternata nella modulazione delle dinamiche neuronali motorie. Nel complesso, questo lavoro contribuisce alla nostra comprensione del sistema del motorio umano, offrendo al tempo stesso nuove conoscenze sull'approccio combinato di tACS e EEG nella caratterizzazione di un ruolo causale delle dinamiche oscillatorie neuronali sul comportamento.

2 STRUCTURE AND FUNCTIONAL MECHANISMS OF ACTION CONTROL

2.1 Control of action in a dynamic environment

2.1.1 Dynamic processes for the rapid control of action

The brain and nervous system are concerned with processing of sensory input, in order to formulate detailed representations of the external environment. Through vision, audition, somato-sensation, and the other senses, we perceive the world and our relationship to it. Sensory receptors provide information about the environment, which is then used to act on the environment. Motor control can be conceptualized as the integration of sensory information, both about the world and the current state of the body, which then activates muscles in order to generate some desired movement or action (Scott, 2004). A feature of this control is the ability to select a required response among competing alternatives, under conditions of conflict and uncertainty. At higher levels of the brain hierarchy cognitive control emerges and by attention, selection and inhibition, modulates actions. Traditionally, Norman and Shallice proposed a model in which automatic operations are executed via well-rooted schemas without the need for high attention levels and in conditions of conflict between two schemas a contention scheduler mediates the conflict (Norman & Shallice, 1986). According to this model, during conflict, alternative actions are simultaneously activated and during the successful response in a specific situation specific actions and outcomes are linked and less conflict will be elicited the next time in the same situation . Thus, to successfully resolve conflict, inhibition of many options is required. It follows that a necessary pre-requisite for flexible, goal-directed action is the ability to inhibit inappropriate or competing responses even when those competing responses have been activated automatically. Thus, an indispensable aspect of motor control which is of paramount importance to deal with a constantly changing environment is inhibition. This term “inhibition” may seem elusive as it has been used in neuroscience

with many different meanings, ranging from inhibitory mechanisms governing behavioural output, to cellular firing, to enzymes reactions. Here I will use the term response inhibition as employed in the modern field of cognitive neuroscience. Traditionally, models of human information processing have distinguished volitional and automatic inhibition (Schneider, Dumais, & Shiffrin, 1982; Schneider & Shiffrin, 1977; Shiffrin & Schneider, 1984). A recent partially overlapping distinction is between reactive and proactive inhibition. Reactive inhibition is normally prompted by external stimuli while proactive inhibition is prospective and necessitates modification of responses to achieve long terms goals (Marjan Jahanshahi, Obeso, Rothwell, & Obeso, 2015a). In order to study reactive inhibition most studies have employed experimental paradigms (i.e. stop-signal or go/nogo tasks), where participants have to abstain from responding or withhold a response when presented with a specific signal. In these paradigms response inhibition is initiated once the stop signal or nogo stimulus has been recognised. As explained earlier, classical models suggested that this inhibition is voluntary, and is presumably mediated by executive mechanisms in prefrontal cortex (Miller & Cohen, 2001; Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004). With regard to this conceptualization, it has often been argued that inhibitory control processes are generally restricted to stimuli that reach awareness, which are imperative to voluntarily stop the response. From this it has been concluded that subliminally presented stimuli trigger only passive activation, and that for active inhibition to occur, stimuli have to be presented supraliminally.

It follows that automatic and unconscious mechanisms have traditionally been regarded as inflexible and contrasted with intentional, flexible and conscious behaviour. Crucially, recent evidence has challenged the view that inhibitory control is restricted to conditions where stimuli are accessible to conscious awareness. These experiments confirmed that inhibitory processes are active even when response tendencies are triggered by subliminal

stimuli (Sumner & Husain, 2008; van Gaal, Ridderinkhof, van den Wildenberg, & Lamme, 2009). Recently, several lines of research suggest there is substantial overlap between the mechanisms supporting conscious and unconscious control of action. Importantly, it has been shown that nonconscious mechanisms can be activated both by current task goals and by attention and therefore do not occur inflexibly regardless of context (Sumner, 2007). For example, data from several sources have identified the importance of the external context in the priming effect. Masked prime stimuli must be similar to stimuli that are relevant for the task currently being performed to elicit priming effects (Kunde, Kiesel, & Hoffmann, 2003; Naccache, Blandin, & Dehaene, 2002). As evidenced by the 'blindsight' phenomenon, direct perceptuo-motor link allows visual information to directly activate motor responses without conscious processing of the stimulus (Weiskrantz, 1986). It has been demonstrated that despite cortical damage and partial blindness a patient was able to successfully guess the orientation of stimuli without conscious processing of the stimulus. Crucially, when the location of the unseen stimulus was indicated by a preceding attentional cue the patient performed such orientation discrimination faster (Kentridge, Heywood, & Weiskrantz, 2004).

In the clinical domain, there are motor control disorders in which the patient cannot abstain from making undesirable movements, as if they were automatically activated without the possibility of being stopped. Such an unconscious and automatic activation of the motor response system does not necessarily require stimuli to be consciously perceived. Thus, while there may be differences between automatic and voluntary processes, they might not be entirely distinct in the brain. It has been shown that automatic processes can be modulated by contextual information and attention, and might play a role in conflict resolution and inhibition of actions. The research presented in this thesis will focus on unconscious automatic motor response activation and inhibition. The next paragraphs

summarize the classical experimental task used to measure reactive inhibition of pre-potent responses and in particular focus on explaining in detail the task used to measure automatic response inhibition. Finally, the experimental evidence for the neuronal substrate of automatic motor inhibition will be described.

2.1.2 Experimental paradigms for measuring rapid control of action

The adoption of sophisticated experimental paradigms in psychology provides a measure of the hypothetical cognitive functions. To measure the processes of inhibition clever paradigms have been developed to investigate constructs such as inhibition and response conflict. Most of previous investigations have adopted task in which the participants are required to voluntarily inhibit a response to specific stimuli (see Table1, for review see Jahanshahi, Obeso, Rothwell, & Obeso, 2015b).

COGNITIVE TASKS	QUANTITATIVE MEASURES	RELATED PROCESSES
Stroop (*Stroop, 1935*)	Reaction Times and errors during interference and control conditions	Inhibition and conflict resolution of prepotent responses of reading the word
Simon (*Simon and Rudell, 1967*)	Differences of reaction times between compatible and incompatible stimuli	Inhibition and conflict resolution elicited by incompatible features of the stimulus
Go\ No Go (*Donders, 1969*)	Errors in noGo stimuli and reaction times	Inhibition of action on specific (noGO) stimuli
Eriksen Flanker Task (*Eriksen and Schultz, 1979*)	Differences of reaction times between compatible Vs incompatible stimuli and errors	Inhibition of the action elicited by contended stimulus characteristics
Antisaccade task (*Fischer and Boch, 1983*)	Differences in reaction times between antisaccade and prosaccade stimuli and errors	Inhibition of prepotent peripheral distractors
Stop Signal (*Logan et al. 1984*)	Reaction time for Go stimuli and stop signal stimuli and errors	Inhibition of initiated response
Negative Priming (*Tipper, 1985*)	Differences in reaction times between distractors stimuli and other stimuli	Automatic inhibition of distracting stimuli
Hayling test (*Burgess and*	Reaction time for response	Inhibition of prepotent response

Shallice, 1997)	initiation and errors	
Random number generation (*Jahanshahi et al., 1998*)	Measure of strategic counting against habitual counting	Inhibition of habit to count in series

Table 1:*Classical experimental paradigms in chronological order that have been developed to measure response inhibition and response conflict.*

In this thesis, I will use a 'masked prime' version of the Eriksen Flanker Task to investigate the impact of subliminal stimuli on motor response processes. In the paradigm, briefly presented prime stimulus were immediately masked and then followed by an imperative target stimuli requiring a choice response.

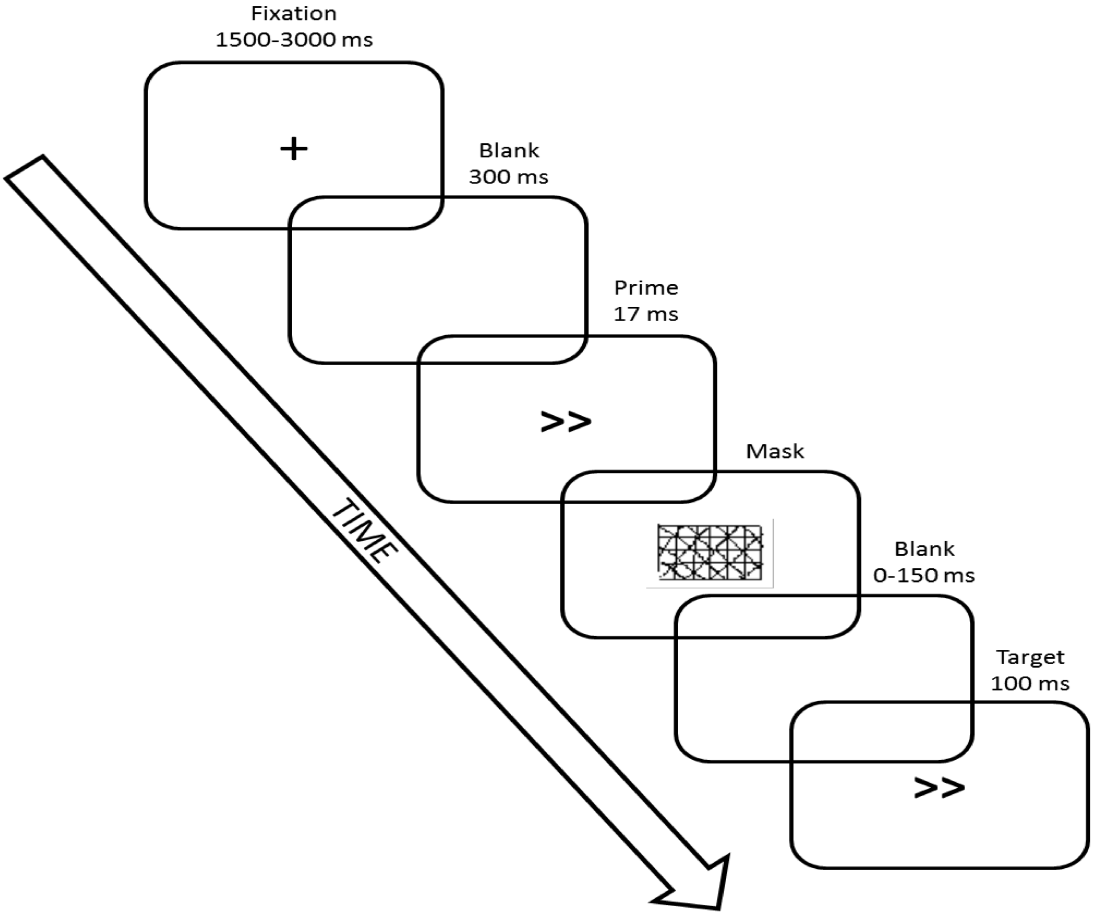


Figure 1: *Schematic illustration of the masked prime task for a compatible trial the duration of the blank screen before the arrow target (0–50–100–150 ms) determined the ISI (100–150–200–250).*

During the task, participants were asked to press a response button as accurately and as quickly as possible with their right hand in response to the appearance of a left-pointing or right-pointing arrow. In each trial, this target stimulus was briefly preceded by a prime stimulus (Figure 1). Whereas the target stimulus is displayed long enough to be consciously perceived, the prime stimulus is not, because its display is short (i.e. 17 ms) and is immediately followed by a backward mask. A high response conflict between left or right responses is expected when the prime and target arrows point in opposite directions (incompatible trials). In each trial, the following stimuli were sequentially displayed on a screen: fixation point, prime, mask, and target stimulus. Each trial started with a central fixation point. Its display was pseudo-randomly jittered between 1500 and 3000 ms. The fixation point display was immediately followed by a blank screen and prime-arrow stimulus, sequentially presented for 300 and 17 ms, respectively. Then, a backward mask and two double target arrows appeared for 100 ms. The mask consisted of 30 randomly oriented lines covering a rectangular area centered on the prime display area on the centre of the screen. Here, there were five main experimental conditions defined by the time elapsed between the mask display onset and the target display onset: 0, 100, 150, 200 and 250 ms. Longer inter stimulus intervals (ISI) were obtained by modulating the time duration of a blank screen presented between the mask display offset and the target display onset. On any given trial, the prime was either mapped to the same response as the target (compatible trial), to the opposite response (incompatible trial) (Tab 2).

CONDITION	**STIMULI**	**AUTOMATIC PROCESSES short ISI**	**AUTOMATIC PROCESSES long ISI**
Compatible	>> \\\\\ >>	*Prime activation*	*Prime activation*
		Response Facilitation	*Prime inhibition*
	<< \\\\\ <<		*Response Conflict*
Incompatible	<< \\\\\ >>	*Prime activation*	*Prime activation*
			Prime inhibition

>> \\\\\ <<	*Response Conflict*	*Response Facilitation*

***Table 2**: Processes induced by the task condition at short (i.e. 0 ms) and longer inter stimuli intervals (ISIs) (i.e.150 ms).*

Negative Compatibility Effect

When the participants performed the task it has been shown that if the interval between the mask and the target stimuli is short (ISI,80 ms), performance (i.e., reaction time (RT)) is faster when prime and arrow stimuli point to the same direction (compatible trials) than in the opposite direction (incompatible trials). This has been traditionally labelled as a positive compatibility effect (PCE). Conversely, when this interval is longer (typically, 100 ms < ISI < 200 ms), a Negative Compatibility Effect (NCE) is observed, namely a performance cost for compatible trials (longer RT, more errors) and a performance benefit for incompatible trials (shorter RT, fewer errors).Table 2 illustrates a summary of the induced automatic processes underlying each condition of the paradigm.

Eimer and Schlaghecken interpreted this effect as an index of the automatic motor self-inhibition mechanism that suppresses the partial motor activation caused by the prime. Thus, this self-inhibition produces a response conflict in the compatible condition, subjects having more difficulties to answer to an arrow which was beforehand suppressed. Eimer and Schlaghecken measuring the lateralized readiness potential (LRP) provided strong evidence indicating this initial effect reversed polarity around 300 ms after prime onset (see chapter 2 figure 8). The LRP revealed an initial activation of the response analogous to the prime followed by a polarity shift, reflecting an activation of the opposite response, reflecting the inhibition of the initial response propensity (M Eimer & Schlaghecken, 1998; Praamstra & Seiss, 2005).The authors argued that, initially the response assigned to the prime is activated, presumably due to a direct perceptuo-motor links which allow sensory information to rapidly affect response processes. The subsequent reversal of these early

effects was interpreted as following inhibition of the initial activation. Indeed, a rapid conduction of information in a direct perceptuo-motor links may allows the system to respond quickly and flexibly to a dynamic environment. Per contra, stimuli that are even inaccessible to conscious perception, have the potential to activate motor responses that interfere with ongoing performance determining imprecise behaviour. Crucially, it has been previously demonstrated that inhibitory processes can be activated in situations where response tendencies are triggered by subliminal stimuli, and that these processes might act to prevent such dysfunctional consequences of a continuous flow of information between perception and action.There has been considerable debate over whether the NCE genuinely reflects automatic inhibitory mechanisms (for review see (McBride, Boy, Husain, & Sumner, 2012). So far, two alternative explanations of the NCE have been proposed. The first, suggest that the NCE occurs because perceptual processing of the target stimulus is slower following a compatible prime, due to habituation-like processes such as "repetition blindness" or an attentional refractory period (Bavelier, Deruelle, & Proksch, 2000; Huber, Shiffrin, Lyle, & Quach, 2002; Lleras & Enns, 2004; van Leeuwen & Lachmann, 2004). On the one hand, it has been demonstrated that such perceptual processes might have a role in generating some reversed priming effects. On the other hand, Boy and Sumner (2010) found that when participants learned novel sensorimotor associations, and those response mappings were unanticipatedly switched, positive and negative priming effects temporarily reversed indicating that the old response mappings continue to be primed until the participants learn the new mappings sufficiently well. Thus, the habituation of perceptual processes of inverse priming cannot explain this finding (Frederic Boy & Sumner, 2010).

The second, suggested that perceptual interactions between the prime and the mask could end up causing motor priming in the opposite direction to that expected from the prime.

This idea has been variously termed “object-updating,” “active mask,” or “mask- induced priming” (Sumner, 2007). Early examples of research into NCE included masks that were constructed by superimposing features of the alternative primes. In this case the most visually salient features of the mask could be those that were new onsets in the stimulus sequence— i.e., those that were not in the prime. Thus, the prime-mask sequence could actually prime the response opposite to the one associated with the prime. Therefore, object updating may play a strong role in producing the NCE when masks are constructed from prime features, but they cannot account for the NCE in other cases where masks do not contain elements of possible primes (Sumner, 2008).

Crucially, the NCE with subliminally presented primes provides evidence that the mechanisms at its origin are deployed automatically. In the subliminal paradigm the instructions are to respond to the target stimuli and the participants are not aware of the prime. It follows that they cannot volitionally suppress any motor response associated with the prime. Differently from paradigms such as go/no-go or stop signal, in which the participants are instructed to abstain the response to specific visual targets or when a sound is presented. Therefore, the motor activation and inhibition mechanisms involved in masked priming can be considered automatic, rather than due to top-down or executive control. Thus far, I have argued that while there may be differences between automatic and voluntary control, they may not have entirely distinct neuronal substrates and that automatic processes may play a role in all behaviour. The following chapter describes the neuronal substrate of action control.

2.2 Structural and functional neuronal connectivity features of action control

2.2.1 Basal Ganglia as a fundamental neural substrate for action control

The basal ganglia (BG) comprise a collection of nuclear structures deep in the brain that have been characterized anatomically and functionally (Parent & Hazrati, 1995; Wilson, 2004). Fronto-striatal-pallido-thalamo-cortical circuits by a balance between inhibition and disinhibition, support adaptable interactions which under conditions of conflict and uncertainty quickly permit to select a required action among alternatives and have a key role in habit formation (Redgrave, Prescott, & Gurney, 1999; Yin & Knowlton, 2006). The next paragraphs describe the neuronal substrate underlying the control of action in a dynamic environment.

General Anatomy of the Basal Ganglia

Anatomically, the BG are interconnected subcortical nuclei inclusive of the striatum (which includes the caudate and putamen), the substantia nigra (SN; including the pars compacta (SNc) and the pars reticulata (SNr), the subthalamic nucleus (STN) and the globus pallidus (GP; comprising the internal segment (GPi) and the external segment (GPe)(Wilson, 2004).

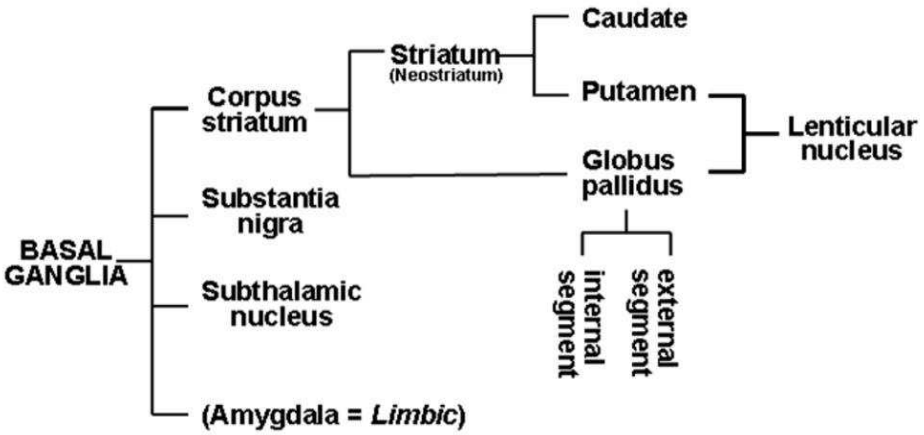


***Figure 2**: schematic classification of the Basal Ganglia.*

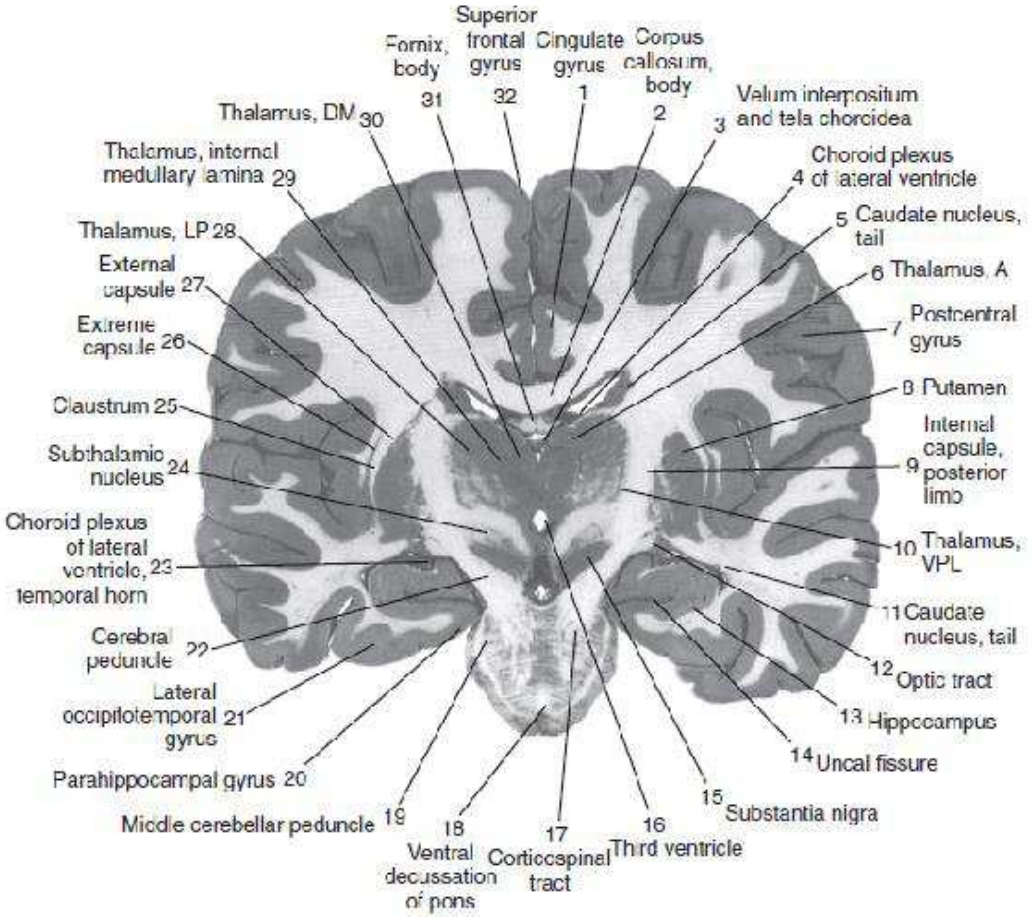


Figure 3*: coronal section of the brain with most of the basal ganglia nuclei. A, anterior nucleus; DM, dorsomedial nucleus; LP, lateral posterior nucleus; VPL, ventral posterior lateral nucleus. adapted from* (Woolsey et al., 2008).

The different parts of the striatum have diverse functions related to different connectivity with the rest of the brain. The putamen is the motor part, the caudate is the associative or cognitive part, and the ventral striatum, which includes the nucleus accumbens (NAcc), is the limbic part. The majority of cells in the striatum (80–95%) are medium spiny neurons (MSN) (Lim, Kang, & McGehee, 2014). The globus pallidus (GP) is divided into the dorsal part and the ventral part and into the internal and external divisions, GPi and GPe, respectively and most neurons in the GP are GABAergic with large arbors of dendrites (Jaeger & Kita, 2011; Kita, 2007). In the STN the major part of neurons are glutamatergic

with long dendrites (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004). The dorsolateral part of the STN is motor, whereas the ventral part is associative and the medial part projects to limbic areas (Benarroch, 2008). The majority of the neurons of the SNc are dopaminergic and are the cells of origin of the nigrostriatal projection. It is clear that the SNc facilitates movement, and there is good evidence as well for a role of dopaminergic system in facilitating specific reward seeking behaviours. These cells contain neuromelanin which makes them dark, giving rise to the name of the nucleus ("nigra") (Sulzer et al., 2000). The connectivity of the BG is critical and complex and some general model for how they are interconnected have been proposed by Alexander, De Long and Strick (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). Five main circuits connecting the BG to the cerebral cortex have been described. In brief, the *motor* circuit links putamen to primary motor cortex (M1) and supplementary motor area (SMA); the *limbic* circuit connects the ventral part of the striatum to the anterior cingulate cortex (ACC); the *associative circuit* links dorsolateral caudate and the dorsolateral prefrontal cortex (DLPFC); the orbitofrontal cortex (OFC) is connected to the ventromedial caudate; the *oculomotor circuit* connects the frontal eye field (FEF) and the caudate body. The following paragraphs summarize the main afferents and efferents of the BG.

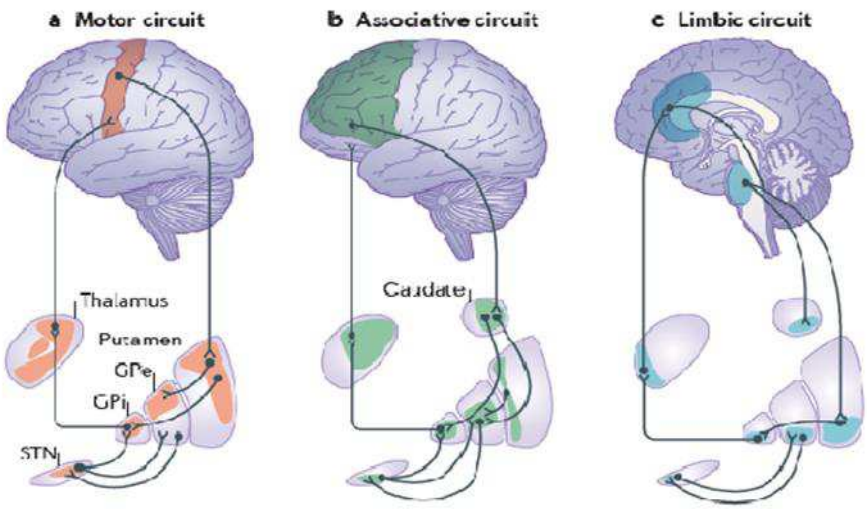


Figure 4: *functional subdivisions in the sensorimotor, associative and limbic cortico–striatal circuits (adapted from* (Rodriguez-Oroz et al., 2009).

Afferents of Basal Ganglia

The striatum is the major input source of the BG it receives projections from the entire cerebral cortex, brainstem, and intralaminar nuclei of the thalamus. The projections from different cortical areas are segregated. The primary motor cortex (M1) and the primary somatosensory cortex project predominantly to the putamen and the premotor cortex and supplementary motor area (SMA) to the caudate head. The frontal lobe projects to the caudate head and the putamen; the temporal lobe to the caudate tail, the parietal and occipital lobes to the caudate body. The enlarged head of caudate reflects the large projection from the frontal cortex to the caudate (Nauta & Domesick, 1984; Parent & Hazrati, 1995). The subthalamic nucleus is also another input area of the BG and via the hyperdirect pathway receives inputs from cortical regions including the SMA, dorsal premotor cortex, anterior cingulate, the dorsolateral prefrontal cortex and the inferior frontal cortex (Nambu et al., 2002)

Efferents of Basal Ganglia

The globus pallidus internal segment (GPi) and the substantia nigra pars reticulate (SNr) are the major output regions of the BG. Both structures form inhibitory GABAergic connections on their targets. The GPi projects to a number of thalamic regions by two fiber tracts: the ansa lenticularis and the lenticular fasciculus. The loop that processes sensorimotor information from the motor cortex and somatosensory cortex projects to the ventral anterior (VA) and the ventral lateral (VL) nuclei. The loop the processes other neocortical information projects to the dorso medial (DM) and parts of the VA nucleus (Parent & Hazrati, 1995).

Intrinsic connectivity and neurotransmitters

The GABAergic striato-pallidal pathway forms inhibitory connections between the striatum and both segments of the GP. The GABAergic striato-nigral pathway forms inhibitory connections between the striatum and the SNr. The globus pallidus external segment makes GABAergic, inhibitory connections with the subthalamic nucleus. The subthalamic nucleus makes glutamatergic, excitatory connections onto both segments of the GP and the SNr. This pathway is the sole excitatory pathway among the intrinsic pathways of the BG. The nigrostriatal pathway has dopaminergic synapse with the striatal neurons.

Three major circuits projecting to the thalamus

Detailed anatomical models of the intrinsic circuitry of the BG have been developed. In this model two pathways that have opposite effects on thalamic target structures have been described. In the direct pathway cells in the striatum that make inhibitory connections with cells in the GPi. The GPi cells in turn make inhibitory connections on cells in the thalamus. Thus, the firing of GPi neurons inhibits the thalamus, making the thalamus less likely to excite the neocortex. When the direct pathway striatal neurons fire, however, they inhibit the activity of the GPi neurons. This inhibition releases the thalamic neurons from inhibition (i.e., it disinhibits the thalamic neurons), promoting them to fire to excite the cortex.

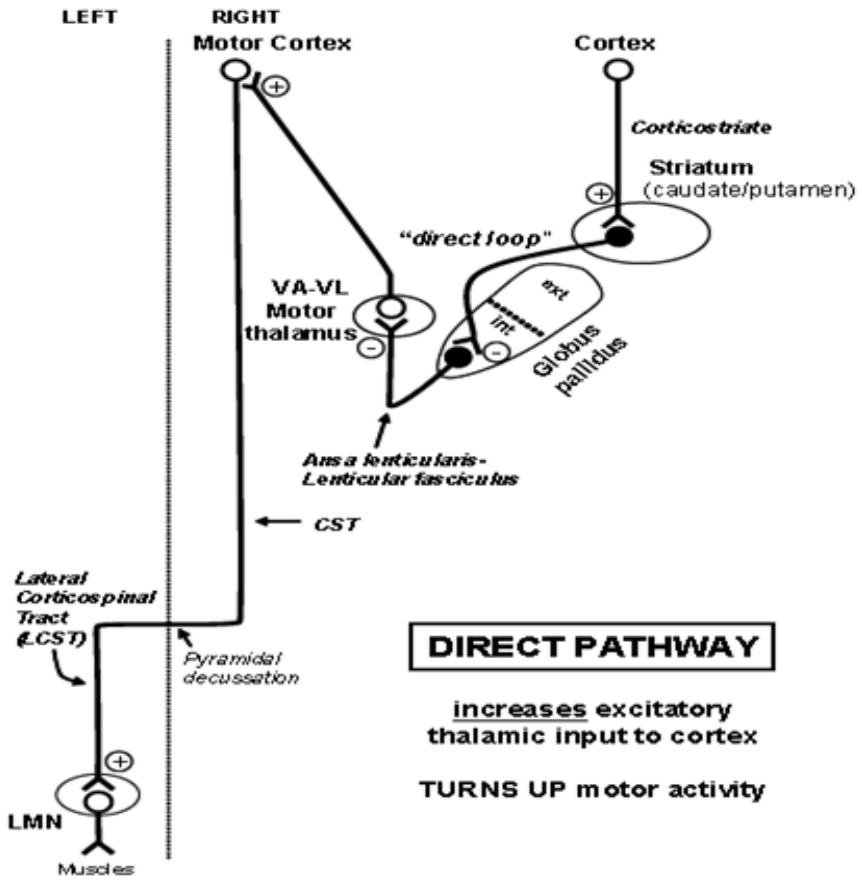


Figure 5a*: schematic representation of the direct pathway.*

In the indirect pathway neurons in the striatum make inhibitory connections to the GPe. The GPe cells make inhibitory connections to the subthalamic nucleus, which in turn make excitatory connections to cells in the GPi. As pointed earlier, the GPi neurons make inhibitory connections on the thalamic neurons. When the GPi cells are active, they inhibit thalamic neurons, thus making the cortex less active. When the subthalamic neurons are firing, they increase the firing rate of GPi neurons, thus increasing the net inhibition on the cortex.

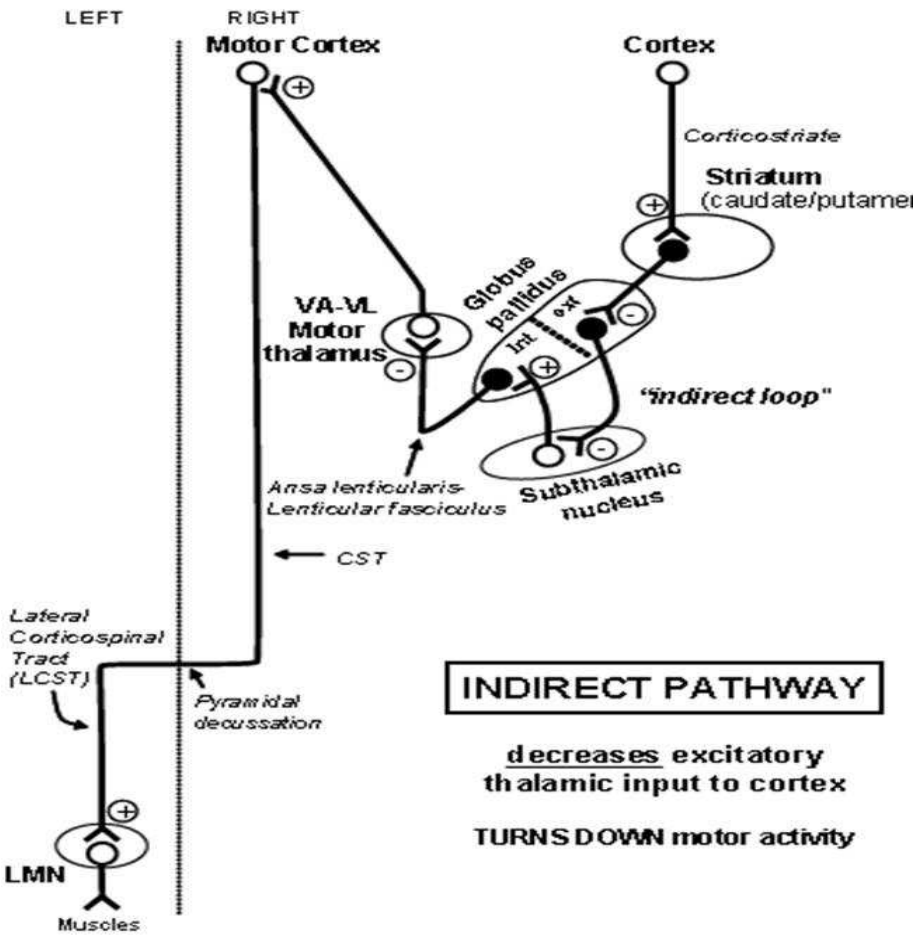


***Figure 5b**: schematic representation of the indirect pathway.*

Furthermore, based on anatomical findings it has been proposed an 'hyperdirect pathway' between the cerebral cortex and STN . This 'hyperdirect' pathway exerts strong excitatory effects on the output nuclei of the BG. This pathway is faster in signal conduction from the cerebral cortex than the 'direct' and 'indirect' pathways. Nambu and collaborators (Nambu et al., 2002) proposed a functional explanation, when a voluntary movement is about to be started, a sequence of signal is sent simultaneously from the motor cortex to the GPi through the cortico-STN-pallidal 'hyperdirect' pathway to activate GPi neurons extensively, thereby resulting in the inhibition of large areas of the thalamus and cortex that are related to both the selected motor program and other alternative competing

program. Confirmatory evidence for the hyperdirect pathway has been recently demonstrated by Akram and colleagues by a probabilistic tractography analysis they characterized the cortical connectivity pathways from STN to the cortex (Figure 6) (Akram et al., 2017).

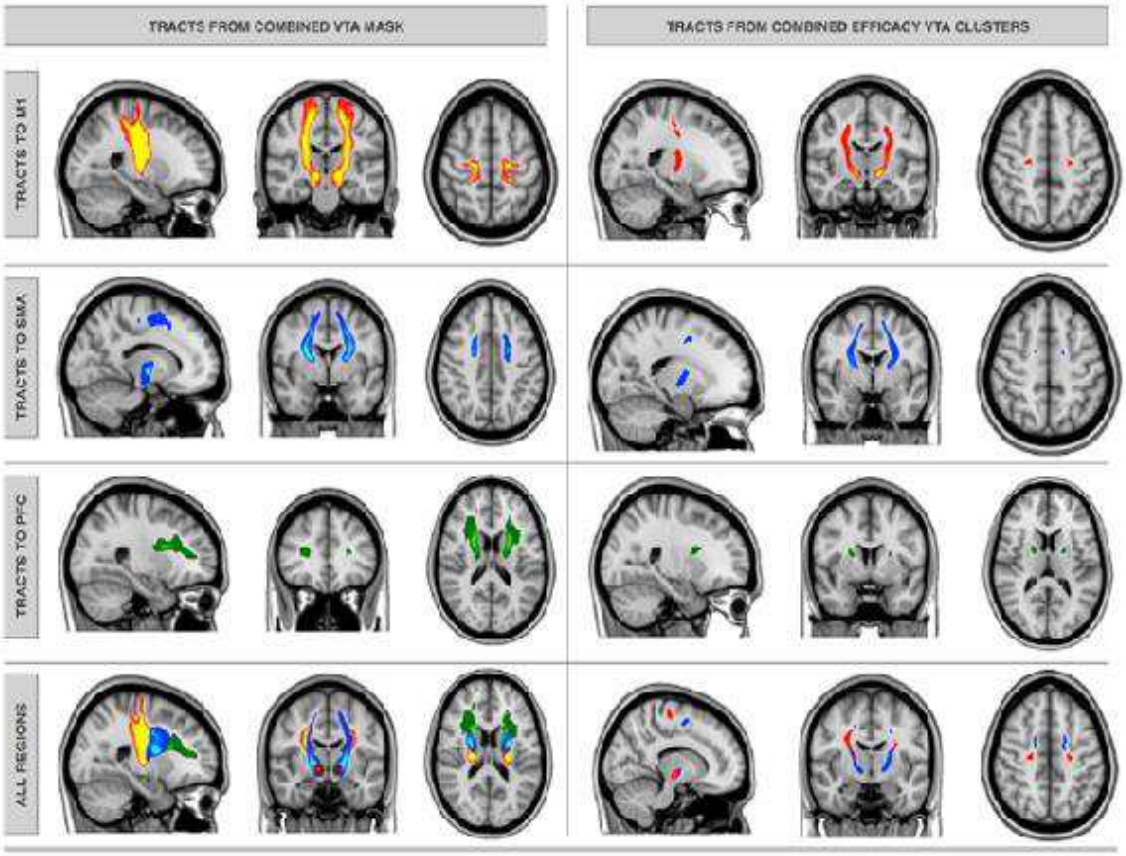


Figure 6*: probabilistic tractography analysis charachterized the cortical connectivity pathways from STN to the cortex (adapted from Akram, 2017).*

The following section outlines the structures of the BG and the cortex that seem to be cardinal in the automatic control of action. On the one hand, the inferior frontal cortex (IFC) has been considered an important node for voluntary reactive inhibition (e.g. stop signal and go/noGo) (Aron, 2007; Wessel & Aron, 2017). On the other hand, there is no evidence for the activation of the IFC during automatic unconscious response elicited by the masked priming paradigm (D'Ostilio et al., 2012; D'Ostilio & Garraux, 2012).

Moreover, the specific role of IFC in reactive inhibition is still under debate. Some authors suggest that IFC has an inhibitory role (Chambers et al., 2007), while others argue that the IFC activity relates to exerting attention to salient stimuli (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). As explained earlier, in the experimental part of this thesis I have adopted the masked prime paradigm, which has been shown specifically to elicit activation in the BG and the SMA (D'Ostilio et al., 2012; Sumner et al., 2007) .Therefore, for the sake of clarity, IFC will not be discussed in detail in the next paragraphs (for review see (Aron, 2007; Wessel & Aron, 2017).

Subthalamic nucleus (STN)

Anatomy and connections

The subthalamic nucleus (STN) is composed principally of excitatory glutamatergic neurons and has been regarded as an important structure in modulation of activity of output BG structures and has been implied in the pathophysiology of Parkinson's disease (PD).

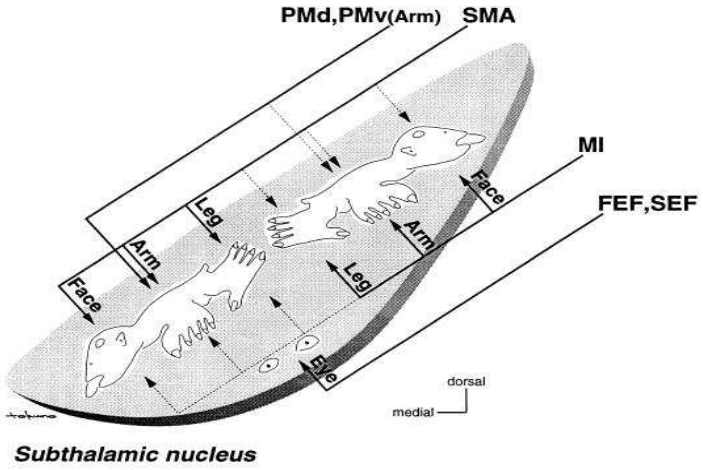


Figure 7: *Schematic diagram showing the organization of cortico-subthalamic (STN) inputs from the primary motor cortex (MI), the supplementary motor area (SMA), the dorsal (PMd) and ventral (PMv) divisions of the premotor cortex, the frontal eye field (FEF), and the supplementary eye field (SEF)* (adapted from Nambu et al., 2002).

STN afferent inputs (Steiner & Tseng, 2017)

Most of the cortical afferents to the STN arise from several motor areas such as the primary motor cortex (M1), supplementary motor area (SMA), pre-SMA, and premotor cortices. The M1 provides somatotopic projections related to the leg, arm and face predominantly to the lateral part of the STN, whereas the SMA projects mainly to its medial counterpart.

STN efferent projections

The STN projects broadly, sending dense projections to the GPi, SNr, and reciprocal projections to GPe, GPi and SNr. Aside from the main efferent projections described above, the STN also send projections to the ventral tegmental area (VTA) in rodents and non-human primates (Parent and Hazrati, 1995).

Functions of subthalamic nucleus (STN)

In the context of the traditional models of BG connectivity increased firing in the STN led to a inhibition of the motor cortex. Anatomical and computational models propose that when stop signals, conflict signals, or surprising events recruit the STN it activates BG output nuclei, transiently inhibiting thalamo cortical projections (Wiecki & Frank, 2013). Recent reviews highlighted convergent evidence that supports the STN's crucial role in reactive inhibition, suppression of unwanted information and switching between responses (Jahanshahi et al., 2015a).

Experimental Evidence from animal studies:

Early examples of animal research includes the work of Baunez et al. that demonstrated that lesioning of the STN in rats speeds up responses but reduces the ability to withhold the response resulting in impulsivity. (Baunez, Nieoullon, & Amalric, 1995). More recently, Wiener et al using the excito-toxic lesion approach, to demonstrate increased impulsivity

and perseveration after lesions of the STN (Wiener, Magaro, & Matell, 2008). In non-human primates STN electrical activity is increased in two types of tasks that putatively involve response inhibition and response conflict : saccade countermanding and go/no-go (Isoda & Hikosaka, 2008).

Experimental Evidence from Deep brain stimulation (DBS) of STN and subthalamotomy in Parkinson's Disease (PD) patients:

Deep brain stimulation (DBS), applying high-frequency electrical stimulation to the STN, has now provided an effective therapeutic option for treatment of Parkinson's Disease (PD). A recent review highlights that PD patients who undergo STN-DBS show impaired performance on various tasks that engage inhibitory control. Using a DBS ON/OFF methodology when patients perform a Go–NoGo task they commit more errors in the DBS ON condition (Hershey et al., 2010). Furthermore patients have more errors when their stimulators are turned ON during the performance of the interference Stroop task (Jahanshahi et al., 2000; Witt et al., 2004). More evidence for the role of STN in response inhibition comes from a recent study that compared PD patients treated with left or right sub-thalamotomy with non operated patients and controls. Using a drift diffusion model the authors demonstrated that STN is involved in response inhibition, specifically tuning the rate of information accumulation and the response threshold and balancing speed and accuracy of performance (Obeso et al., 2014). Crucially, Fife and collaborators (Fife et al., 2017), using an optogenetic approach, recently provided strong evidence that the STN is essentially involved in the inhibition of actions. In particular, they showed that behaviour can be rapidly and potently interrupted by transient increases in STN output .

Supplementary motor complex (SMA, pre-SMA, SEF)

Anatomy and connectivity of supplementary motor complex (SMC)

The supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA) are based in the superior frontal gyrus anterior to the leg representation of the primary motor cortex. The supplementary eye field (SEF) divided the SMA and the pre-SMA adjacent to the paracentral sulcus. All these interconnected areas are part of the supplementary motor complex (SMC). These are adjacent to the cingulate sulcus and gyrus, including the 'anterior cingulate cortex' (ACC) (Goldberg, 1985; Nachev, Kennard, & Husain, 2008).

Using electrical stimulation on the brain it has demonstrated that SMA, similarly to the STN, is functionally organized like a somato-topically arranged map of the body (Fried et al., 1991). Subsequently, Matsuzaka and colleagues on the basis of functional findings have separated SMA and pre-SMA, the electrical excitability of the SMA is greater than that of the pre-SMA (movements are evoked more easily in the SMA)(Matsuzaka, Aizawa, & Tanji, 1992). Further studies have shown that the SMA has direct connections with spinal motor neurons, particularly those innervating muscles of the fingers and wrist providing direct and substantial projections to the corticospinal tract (Jenny, Inukai, & Strick, 1983). Moreover, the pattern of termination of SMA corticospinal cells resembles that of primary motor cortex projections. Crucially this suggest that SMA cells are directly connected to motor neurons. Pre-SMA and the SEF project to the dorsolateral prefrontal (DLPFC) cortex. Interestingly, whereas the SMA has reciprocal connections with the primary motor cortex, the pre-SMA does not. This evidence supports the direct contribution of SMA to motor output as compared to the pre-SMA and the SEF which are indirectly related to the motor output.

Connectivity

All parts of the SMC are connected with the BG. The SMA, the pre-SMA and the SEF all send efferents to the striatum, which projects onto the GPi both directly and indirectly. Thus, these pathways complete a key cortico–basal ganglia loop. Crucially, both the SMA and the pre-SMA have a 'hyperdirect' connection to the STN assigning this pathway a pivotal role in control of actions (Akram et al., 2017; Nambu et al., 2002).

2.2.2 Experimental evidence of the neural substrate of automatic unconscious inhibition

Negative compatibility effect (NCE) as an index of automatic motor control

Originally, Eimer and Schlaghecken reported a reversal of masked response priming effects when a delay is introduced between the priming stimulus and target stimulus. When the interval between the mask and the target stimuli is short (the inter stimulus intervals (ISI) < 80 ms), reaction times (RT) are faster when prime and arrow stimuli point in the same direction (compatible trials) than if they point in the opposite direction (incompatible trials). On the other hand, if the interval is longer typically, 80 ms < ISI < 250 ms), the effect reverses (negative compatibility effect (NCE)) so that compatible trials have a longer RT than non-compatible trials (for review see (Martin Eimer & Schlaghecken, 2003).

The following section summarizes the experimental evidence which adopted the masked-prime task with manual responses, based on the original paradigm developed by Eimer and Schlaghecken (Figure 1).

Empirical Evidence of Negative Compatibility Effect

Early examples of research into the negative compatibility effect (NCE) demonstrated that NCE is reflected in movement-related electroencephalogram recordings of the lateralized

readiness potential (LRP) as a fast alternation between activation states that facilitate correct and incorrect response alternatives (Eimer & Schlaghecken, 1998; Praamstra & Seiss, 2005). It has been proposed that the multiphasic shifts of motor cortex activation between correct and incorrect response alternatives might clarify the dynamics of motor cortex activation during response conflict. Similarly, partial activation of an incorrect response and the consequent competition with the correct response are related as determinants of reaction time and error patterns in the interference tasks (see Table 1). such as the Stroop task (color–word interference; Stroop, 1935), the Eriksen flanker task (flanker compatibility; Eriksen & Eriksen, 1974), or the Simon task (spatial stimulus–response compatibility; Simon & Rudell, 1967).

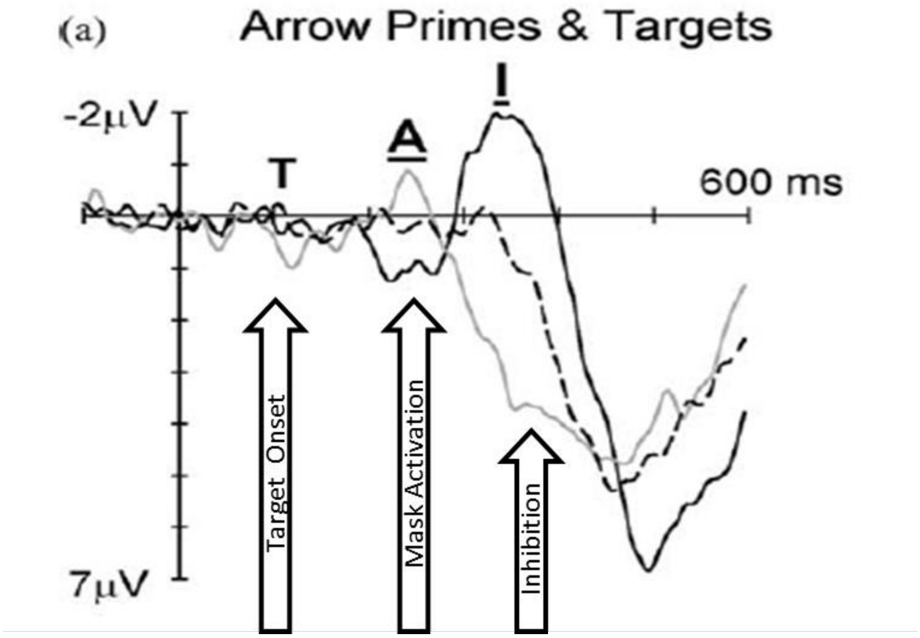
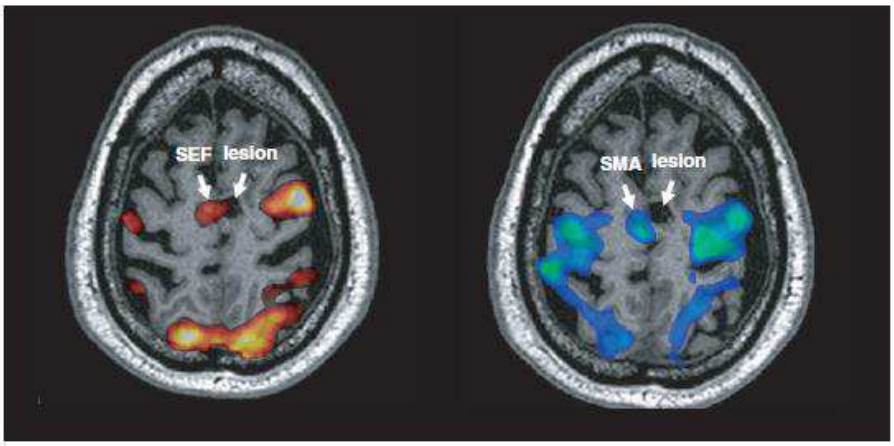


Figure 8*: LRP waveforms measured in compatible, incompatible, and neutral trials, displayed relative to the onset of the masked primes. 'T' indicates the onset of the target stimulus. Downward-going (positive) deflections indicate activation of the correct response, upward-going (negative) deflections reflect a relative activation of the opposite response. 'A' indicates the initial response activation triggered by the masked primes, 'I' marks the subsequent inhibition of this response activation (M Eimer & Schlaghecken, 1998).*

Studies of brain lesion due to stroke can provide evidence for a loss of function due to a specific lesion in a circumscribed area. In this regard Sumner and collaborators provided a

key causal evidence that supplementary motor area and supplementary eye field (SMA and SEF) may contribute to voluntary control by automatic inhibition of unwanted motor plans. Two patients with small microlesions of SMA and microlesions of SEF failed to show NCE reflecting an absence of automatic inhibition as evoked by masked prime stimuli (Figure 8) (Sumner et al., 2007). The authors demonstrated that there is an overlap between the cortical areas crucial for implementing automatic control and those associated with voluntary control. More evidence demonstrated that the SMA and nearby pre-SMA are involved in producing the NCE . A recent study using voxel-based morphometry analysis found that individual differences in pre-SMA gray matter were correlated with participants' ability to correctly respond to a target that had been preceded by a strongly masked incompatible prime (van Gaal, Scholte, Lamme, Fahrenfort, & Ridderinkhof, 2011).



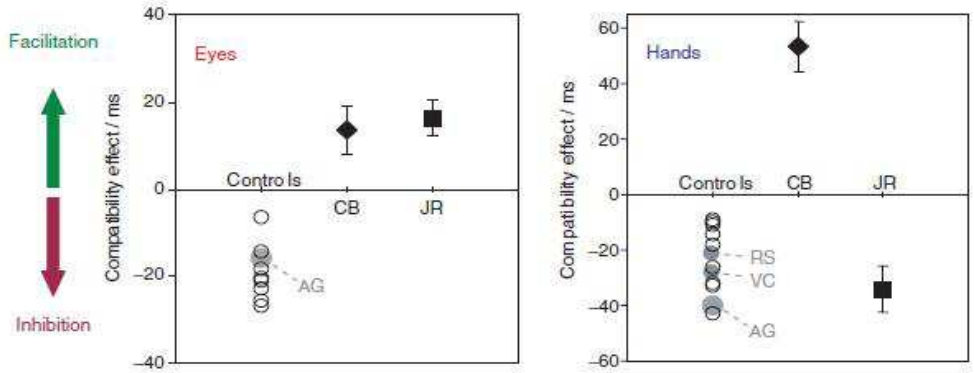


Figure 9*: Top: MRI scan of one patient (CB), with superimposed activity from fMRI in which the patient moved his eyes (left image) or moved his fingers (right image). Lesion in the right hemisphere can be localized with respect to the functional activation of the SEF and SMA in the opposite hemisphere, and it can be seen that the lesion has affected both right SEF and right SMA but does not extend beyond these areas. Bottom: compatibility effects for the masked prime task. Control group showed negative compatibility effects (NCEs) for both saccadic and manual responses, but CB produced positive compatibility effects instead. Patient JR, who has an small on the SEF, showed the normal effect for manual responses but was abnormal for saccades, like CB. Therefore, the inhibition seems to be effector specific. Adapted from* (Sumner et al., 2007)*.*

Furthermore, Boy et al. by a combined fMRI subliminal masked task paradigm, showed a modulation of BOLD signal in the SMA during the subliminal inhibition task (Frédéric Boy, Husain, Singh, & Sumner, 2010). In line with this evidence, it has been shown by magnetic resonance spectroscopy (MRS) that the concentration of gamma-aminobutyric acid (GABA) in the SMA was correlated with the magnitude of the NCE (Figure 10) Boy et al. (Frederic Boy et al., 2010).

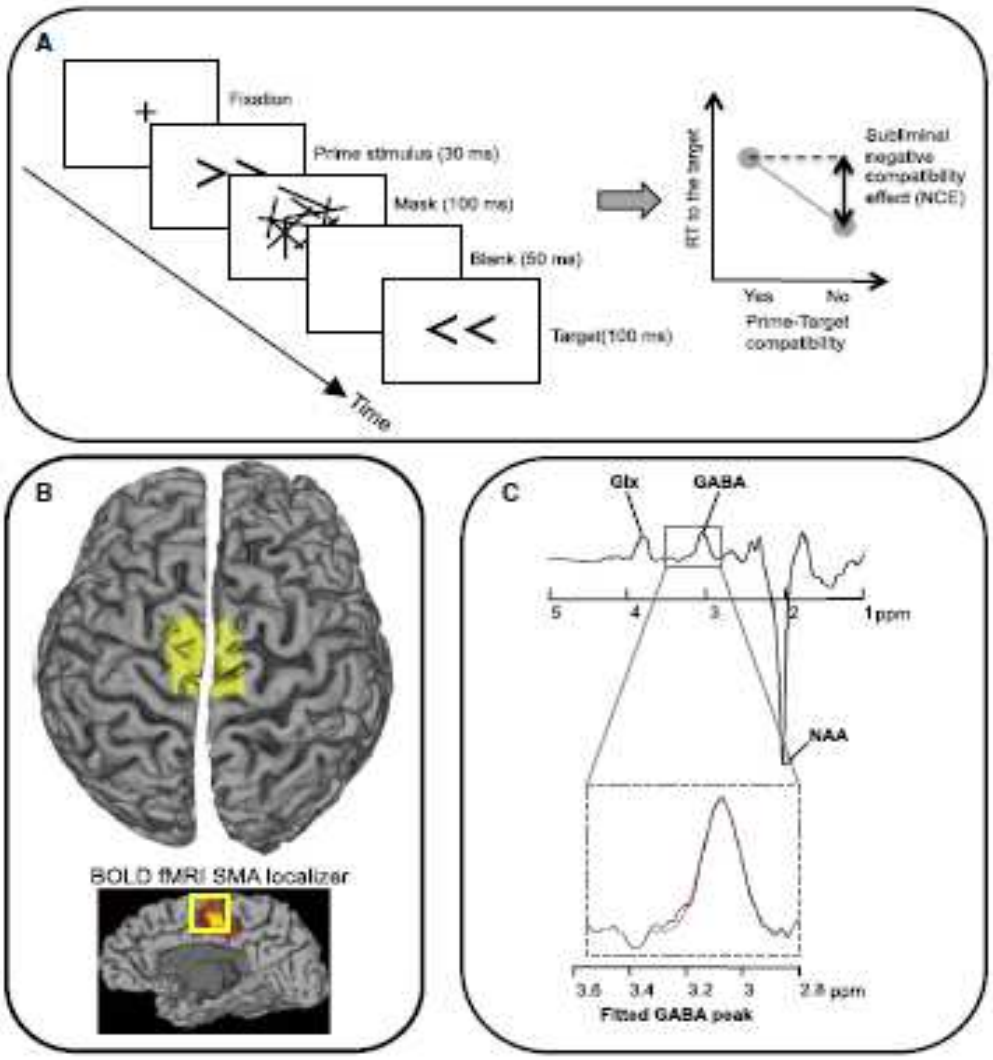


Figure 10: *(A) Behavioural paradigm. (B) The MRS voxel (yellow, [3 cm]3 voxel) was placed over the anatomical location of SMA. (C) quantification of GABA concentration by extracting the area under the GABA peak (adapted from* (Frederic Boy et al., 2010).

More recently, by functional magnetic resonance imaging (fMRI) D'Ostilio and collaborators (2011) demonstrated that SMA activity is involved in the processing of motor plans automatically elicited by unconsciously perceived visual stimuli, even if the corresponding plans are not executed. Moreover, D' Ostilio and colleagues have reported for the first time activity changes in the SMA and the striatum that closely match the negative compatibility effect (NCE) (D'Ostilio et al., 2012). The findings showed that the inhibition induced by the prime activated a part of the premotor cortex but no prefrontal areas. This led the authors to argue that this unconscious and automatic inhibition is a basic motor process allowing preparatory mechanisms to automatically suppress an activated movement without the need of cognitive processes (for review see (D'Ostilio & Garraux, 2012).

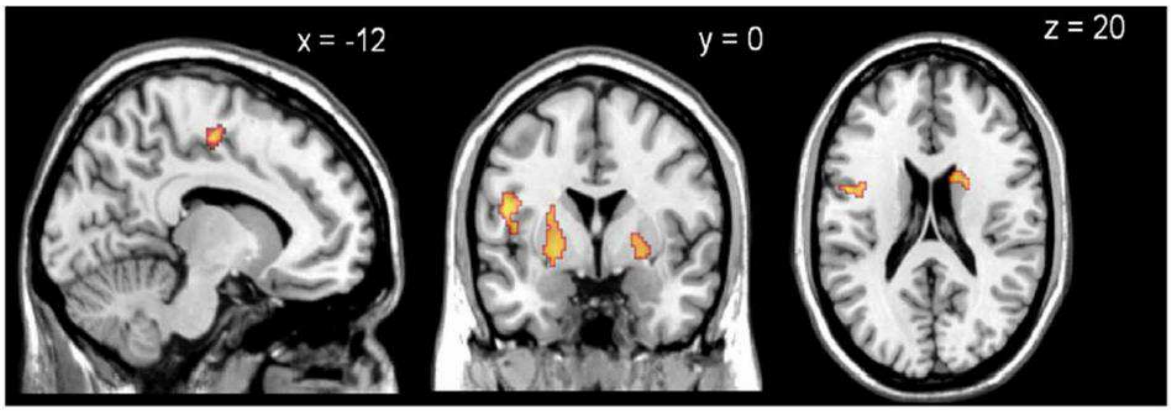


Figure 11*: Results of parametric fMRI analysis. The behavioral pattern of PCE/NCE was associated with a similar pattern of activity changes in the premotor cortex, especially the SMA, the caudate and the putamen (p,0.005 for display purpose) (D'Ostilio et al., 2012).*

The previous section has shown that converging evidence using different methodology suggests the activation of a cortico-BG network and in particular the activation of the SMA

as an important signature for the automatic inhibitory processes related to the control of actions in a dynamic environment.

As was pointed out in the introduction subliminal visual stimuli can automatically activate motor plans. Such automatic activations are likely to occur during most behaviours and can be revealed following brain damage. Even if these complex control mechanisms are not completely understood, it appears that unconscious automatic inhibition is essential in all behaviours. This, challenges the distinction between voluntary and automatic control.

In the chapters that follow, I consider the potential functional role of synchronization of neural activity in neuronal information processing. Specifically, different hypotheses regarding the physiological origins and functional relevance of the beta frequency in the cortico-basal ganglia network and its contribution to motor control will be discussed.

2.3 Synchronized beta brain oscillations as a dynamic and flexible feature of the sensorimotor system and beyond

2.3.1 What are oscillations and how we can measure oscillations?

Awareness of brain oscillations is not recent, having possibly first been described in the 19th century by Richard Caton (1842–1926). Using the galvanometer to amplify the tiny voltage signal, Richard Caton was the first to record spontaneous electrical activity in the mammalian brain. A seminal article was published in 1929 entitled 'Uber the electroencephalogram das mensch' by Hans Berger (1873–1941), this was the first document of recordings of neuronal oscillatory activity in humans, using scalp surface electrodes. Berger was the first who characterized the continuous oscillations discriminating between larger and smaller amplitude waves with longer and shorter

duration, and coined them as alpha and beta frequency waves (Berger, 1929). These oscillations which are characterised by their number of cycles per second or frequency, reflect an indirect measure of the synchronous activity of many populations of anatomically aligned neurons**.** During the past 30 years, much more information has become available strongly indicating that oscillatory signals subserve important functions. Ongoing intrinsic and event-related oscillations are conventionally categorized into five frequency bands referred to by letters of the Greek alphabet: delta (0.5–3.5 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13– 30 Hz) and gamma (>30 Hz). A note of caution is due here since, the precise boundaries between different bands are difficult to define and differ considerably between experiments. A large and growing body of literature has investigated the neuronal mechanisms that underlie this oscillatory rhythmical activity (Adrian, 1935; Buzsaki, 2006; Freeman, 1976; Lopes da Silva, 1991). A considerable amount of literature has been published on the interplay between interneurons and pyramidal cells and on the cortico-thalamic loops as central generator of oscillatory activity. Importantly, it has been discovered that synchronous activity of neurons may change locally within a local population of neurons and can also display distinct patterns of synchronization with distant neuronal populations through coherence (Fries, 2005). Fries argues that communication through coherence is possible through cyclic changes in the excitability of local neuronal populations which produce temporal windows for communication. Thus, it has been proposed that synchronization between distant population of neurons can temporally coordinate the information transfer across brain regions because their communication windows for input and for output are open at the same times. Recently intriguing hypotheses have also been suggested on how oscillations may interact across different frequencies through cross frequency coupling (Jensen & Colgin, 2007).

2.3.2 Beta frequency (13–30 Hz) oscillations as an index of sensorimotor processing.

2.3.2.1 Beta as an 'Idling' rhythm in the motor system

Regarding the beta-band (13-30 Hz), many classical proposals have linked this rhythm to motor functions (Jensen, Pohja, & Goel, 2002; Pfurtscheller & Lopes da Silva, 1999). Beta oscillations can be recorded from the motor cortex (S N Baker, Olivier, & Lemon, 1997; Sanes & Donoghue, 1993) and the basal ganglia (Brown et al., 2001; Kühn et al., 2004; Priori et al., 2002). Moreover, corticospinal synchronization is measured in the periphery through the synchronization of motor units within and between muscles (J M Kilner et al., 1999; Salenius & Hari, 2003). Previous research has established that oscillations measured by local field potentials (LFP) arise through the synchronization of populations of local neurons, so that the discharges of single neurons are locked to the oscillations at different levels of the motor system (Stuart N Baker, Pinches, & Lemon, 2003; Donoghue, Sanes, Hatsopoulos, & Gaál, 1998). Importantly, event-related phenomena representing frequency specific changes of the ongoing EEG are measured by a decreases or an increases of power in given frequency bands. This has been ascribed to a decrease or an increase in synchrony of the underlying neuronal populations (Pfurtscheller & Lopes da Silva, 1999). Numerous empirical evidence show the suppression of motor cortex beta (13-30 Hz) bands prior to and during movement followed by a post-movement rebound (Pfurtscheller & Lopes da Silva, 1999). Up to now, data from several sources have identified that movement features such as force and number of muscles involved in a specific movement are related to the strength of the event related desynchronization (ERD) and synchronization (ERS). Increase of the force during movements are characterized by prolonged beta ERS and stronger beta ERD (Mima, Simpkins, Oluwatimilehin, & Hallett, 1999; Stančák, Riml, & Pfurtscheller, 1997). Moreover, beta-ERD increases with multiplicity of sequential finger movements

(Manganotti et al., 1998). It has been show that beta-ERD starts before movements and that it reflects a state of movements preparation (Neuper & Pfurtscheller, 2001). Beta-ERD is lateralized when there is prior knowledge regarding which hand to move and this is reflected in stronger power suppression over the hemisphere contralateral to the response hand. Strength of beta-ERD is also associated with faster response times compared to a non-lateralized ERD. Combining EEG and TMS, Chen and colleagues have shown a decrease in corticospinal excitability during beta-band ERS (Chen, Yaseen, Cohen, & Hallett, 1998). This is in line with the proposed function of beta ERS as a correlate of 'idling' motor cortex following movement execution (Pfurtscheller, Stancák, & Neuper, 1996).

2.3.2.2 *Beta as a dynamic process to maintain the current sensorimotor set*

Studies of cortical beta oscillations in humans suggest that increased physiological levels of beta activity slow voluntary movement. Androulidakis and colleagues demonstrated that up regulation of beta activity prior to a postural task improves behavioural performance, suggesting that the effect of beta synchrony in motor cortex may be the maintenance of steady-state force output (Androulidakis et al., 2007). Related to this phenomenon there is also a specific increase in cortical beta activity for successful stop trials in Go/NoGo-tasks in both human and non-human primates (N. Swann et al., 2009a). Following motor errors increased beta-band rebound has been showed and it has also been interpreted as a signature of increased response inhibition (Koelewijn, van Schie, Bekkering, Oostenveld, & Jensen, 2008). Gilbertson et al. demonstrated that, while actively promoting postural activity, voluntary movements are slowed during periods of high beta (Gilbertson, 2005). A similar argument has been made to account for the slowing of movement execution during application of beta tACS over M1 by Pogosyan and collaborators (Pogosyan, Gaynor, Eusebio, & Brown, 2009).

All these studies indicate that an up-regulation of beta synchrony can be functionally relevant in the sensorimotor system. Taken together, these data are compatible with the hypothesis that beta oscillations may signal the tendency of the sensorimotor system to maintain the status quo (Engel & Fries, 2010a).

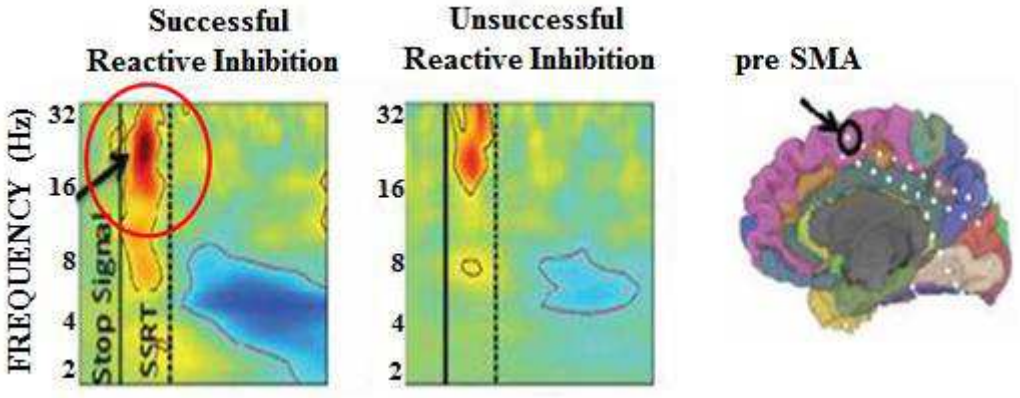


Figure 12: *Intracranial recording demonstrated that beta activity increases in the preSMA following the stop signal (adapted from* (N. C. Swann et al., 2012).

Experimental evidence from subthalamic nucleus (*STN) Synchronized Oscillations in the beta frequency (13-30 Hz)*

Very important are observations on the effect of electrical stimulation through the surgically implanted electrodes in the basal ganglia (BG). Deep brain stimulation (DBS) for treatment of Parkinson's Disease use chronic high-frequency stimulation at pulse rates around 130 Hz is typically applied in the patients (Dayal, Limousin, & Foltynie, 2017). In view of much of the electrophysiological literature on the STN focuses on the presumed anti-kinetic role of beta oscillations in motor networks (Hammond, Bergman, & Brown, 2007), several studies have investigated whether beta oscillations might play a similar role in response inhibition and conflict resolution. Kuhn et al. using a Go–NoGo paradigm demonstrated that during NoGo trials, when the patient has to withhold the response, showed an initial decrease in beta (ERD) activity which is quickly reversed to a relative beta increase (ERS). Inversely Go trials showed event related decrease (ERD) in beta band

activity (Kühn et al., 2004). The author ascribe this increase in beta as functionally relevant to inhibit the response. Similarly, during the stop signal task, stop trials are associated with an increase in beta band activity. Interestingly, also the latency of the beta increase correlated with how fast participants react to the stop signal trials (Ray et al., 2009). Alegre (Alegre et al., 2013) shows that beta oscillations are higher during successful stop trials relative to failed stop trials and that increased STN beta activity is associated with elevated beta band coherence with the motor cortex. To investigate the role of beta oscillations during conflict Brittain and colleagues combined the classical Stroop task with EEG measures. The authors highlighted that high-conflict trials exhibit a similar beta band pattern to that described during stopping tasks. Both low- and high-conflict trials showed a decrease in beta band activity after the stimulus onset, but during high-conflict trials, a small relative increase in beta power took place before the response was made. Notably, during error trials, the beta band increase still appeared, but it occurred after the response was made (Brittain et al., 2012). All in all, these studies suggest that beta oscillations in the STN and connected structures may play an important role in inhibiting movement, particularly during reactive response inhibition. Therefore also these evidence of STN beta activation might be consistent with the hypothesis that beta oscillations may signal the tendency of the sensorimotor system to maintain the current task set. Importantly a recent tractography study demonstrated the connectivity between the STN, the motor cortex and the SMA. It also characterised how DBS stimulation of different location of the STN might have an impact on the clinical motor symptoms of Parkinson's Disease such as bradykinesia and rigidity (Akram et al., 2017).

2.3.3 Dynamic changes in beta oscillations in a wider range of cortical areas beyond sensorimotor control and content specific hypothesis

Thus far, a relationship exists between beta oscillation and the sensorimotor system. Let us now consider the relation between beta oscillations and other cognitive processes. Over the

past decade, most research has emphasized the changes of beta oscillations in areas of the brain other than sensorimotor. Modulations of beta power have been correlated with the visual perceptual processes by motion-induced blindness paradigm (Kloosterman et al., 2015). Donner and colleagues adopting a simple perceptual task have also been demonstrated that beta is higher before correct behavioural choices than before errors. The authors interpreted this as a potential role of beta activity for the efficiency of neural computations (Donner et al., 2007). Recent monkeys studies support the importance of beta oscillations in top-down and bottom-up processes of decision making (Pesaran, Nelson, & Andersen, 2008; Wimmer, Ramon, Pasternak, & Compte, 2016; Wong, Fabiszak, Novikov, Daw, & Pesaran, 2016). Underlying oscillatory neuronal beta activity was identified also in relation to working memory load (Deiber et al., 2007; Siegel, Warden, & Miller, 2009) and language (for review see Weiss & Mueller, 2012). Some mechanistic aspects of beta oscillations have been tentatively identified. In particular, beta oscillations are mostly associated with endogenous, top-down processing (Engel & Fries, 2010a). Furthermore, in line with a "communication through coherence" view (Fries, 2015), oscillations in the beta frequency range are presumed to facilitate long range interactions on a cortical network level (Kopell, Ermentrout, Whittington, & Traub, 2000). Both these aspects have been integrated in a predictive coding framework that is classically implemented using the Bayesian inference. In this framework it is assumed that action and perception both result from an interplay between the top-down sensory predictions and the bottom-up sensory inputs (Adams, Shipp, & Friston, 2013; James M. Kilner, Friston, & Frith, 2007). Bottom-up and top-down influences have been hypothesized to subserve the signalling of prediction errors and predictions, respectively. These concepts are central to the theory of predictive coding, stating in essence that functional hierarchy higher areas of the brain constantly generate predictions based on incoming evidence and prior experience,

and feed those predictions back to lower areas, where they are subtracted from sensory inputs, such that only prediction errors need to be forwarded to higher areas (A. M. Bastos et al., 2012). In other words, to use sensory information efficiently to guide action in the world, the brain must represent sensory information probabilistically and use information about uncertainty regarding perception and action. Recent evidence shows that gamma-synchronization serves feedforward (bottom-up) communication, whereas beta-synchronization affords feedback communication of top-down predictions (M. Bastos et al., 2015). Recently it has been proposed that beta oscillations are content-specific and provides a mechanism for the formation of functional neuronal ensembles during endogenous (re) activation of cortical representations (for review see Spitzer & Haegens, 2017). In line with this interpretation a number of findings indicate that in some task contexts, beta oscillatory activity can be content specific, that is, it can reflect the very information that is currently being processed. Such content-specific beta activity has in particular been observed during endogenous information processing in working memory and decision making. It has been interpret as a role of beta oscillations in endogenous content (re)activation (for review see Spitzer & Haegens, 2017). In sum, there are several accounts aiming to explain the role of beta oscillations. Some accounts focused on the role of beta in the sensorimotor system as an 'idling system' (Pfurtscheller & Lopes da Silva, 1999); others reviewed evidence from recent studies of cognitive processing of the motor system and on the pathophysiology of movement disorders suggesting that beta-band activity relates to maintenance of the current sensorimotor or cognitive states (Engel & Fries, 2010b). Finally, recent work of endogenous information processing in working memory and decision making suggests a role for beta oscillations in endogenous content (re)activation**.** While a unifying theoretical account of cortical beta oscillations is still lacking, some of these lines of research have provided several possible explanations and

candidate mechanisms for the functional role of beta oscillations. This section has attempted to provide a brief summary of the literature relating to human beta oscillations. The next section firstly briefly describes the basic principles of neurophysiology and then went on to describe the methods used in the experimental part of the thesis .

3 NEURONAL CODING AND NON INVASIVE BRAIN STIMULATION

3.1 Basics of neurophysiology

In order to understand the mechanisms by which the non invasive brain stimulation acts, one should know some basic neurophysiological principles underlying the activity of the nervous cell. These cells are specialized in their anatomy and physiology to perform different tasks and they exhibit a voltage difference across the membrane. Changes in the membrane voltage generate an action potential that permits nerve cells and muscle cells to communicate by electrochemical impulses. What follows is a short introduction to the anatomy and physiology of nerve cells.

3.1.1 Neurons

All neurons consist in three main components (Figure 13): the cell *body*, also called the soma; numerous short processes of the *soma*, called the *dendrites*; the single long nerve fiber, the *axon*. Although neurons have the same basic structure and function there are some significant differences between different types of neurons in terms of spatial arrangements of the dendrites and axon (Figure 14).

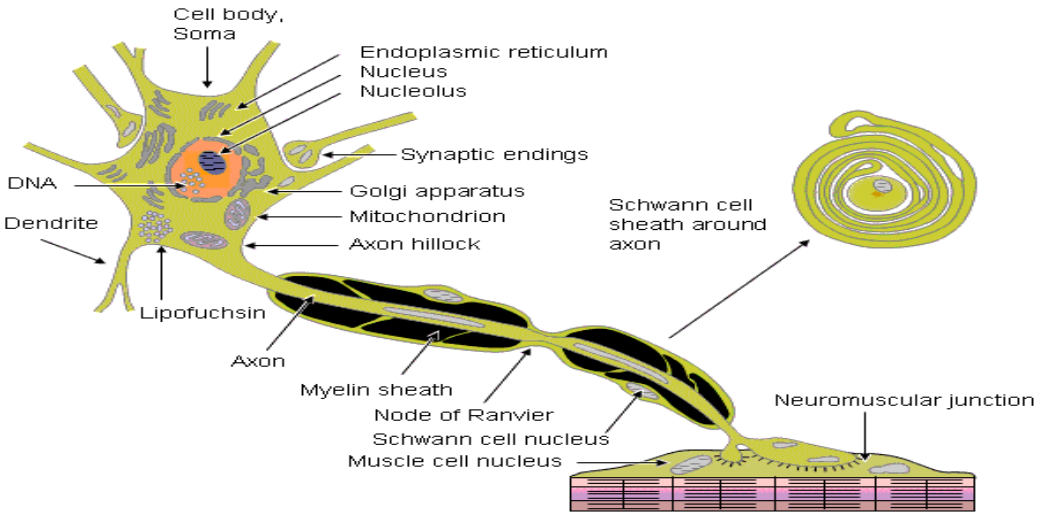


***Figure 13**: schematic representation of a neuron.*

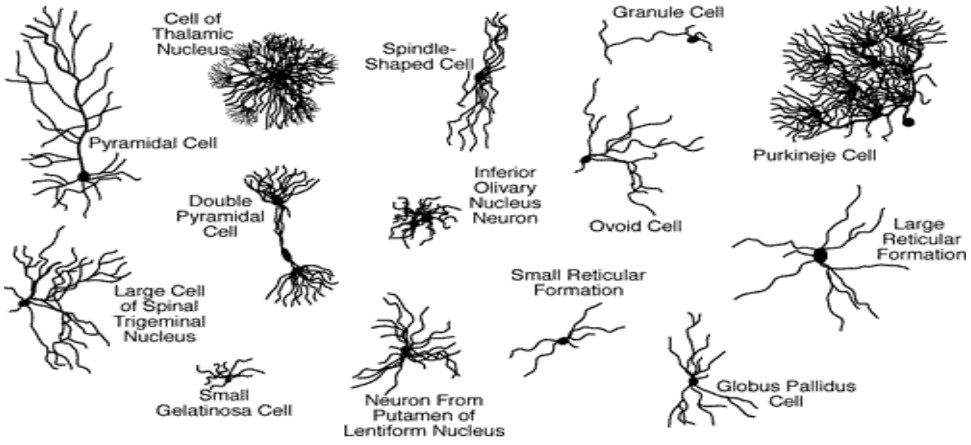


***Figure 14**: Cajal drawings of neurons*.

The dendrites receive impulses from the axons of other neurons and transfer them to the cell body (afferent signals). The effect of these impulses may be excitatory or inhibitory. A neuron may have many thousands of dendrites, but it will have only one axon. At the end of the axon lies the structures that contain neurotransmitters, called the ’axon terminals’’. Neurotransmitters are the chemical medium through which signals flow from one neuron to the next at chemical synapses. For a detailed discussion about neuron structure and function see the book of Kandel and collaborators ‘*’Principle of Neural Science’’*(Kandel, 2013).

3.1.2 Cell membrane

Each neuron is surrounded by a cell membrane that is formed by a phospholipid lipid bilayer with a nonpolar lipid (hydrophobic) tails constituting the middle of the bilayer and a polar phosphate (hydrophilic) heads abutting the extracellular matrix and cytoplasm (Figure 15). Embedded in the lipid bilayer are protein macromolecules, including ion

channels, ligand receptors, and ionic pumps, that are in contact with both the extracellular fluid and the cytoplasm. The lipid bilayer is relatively impermeable to water soluble molecules, including ions such as sodium (Na+), potassium (K+), chloride (Cl-) and calcium (Ca2+). The balance between these ions on the inside outside of the membrane is such that there is normally a resting potential of -70 millivolt across the membrane (Bear et al). These ions are involved in electrophysiological activity and signal transmission. The equilibrium of transmembrane ion concentration depends on the balance between (1) passive diffusion of ions across ion channels, or "pores," of the membrane, driven by their concentration gradient and (2) active, energy adenosine triphosphate (ATP)-dependent transport of ions against their concentration gradient, via ATP-driven ion pumps (Kandel, 2013).

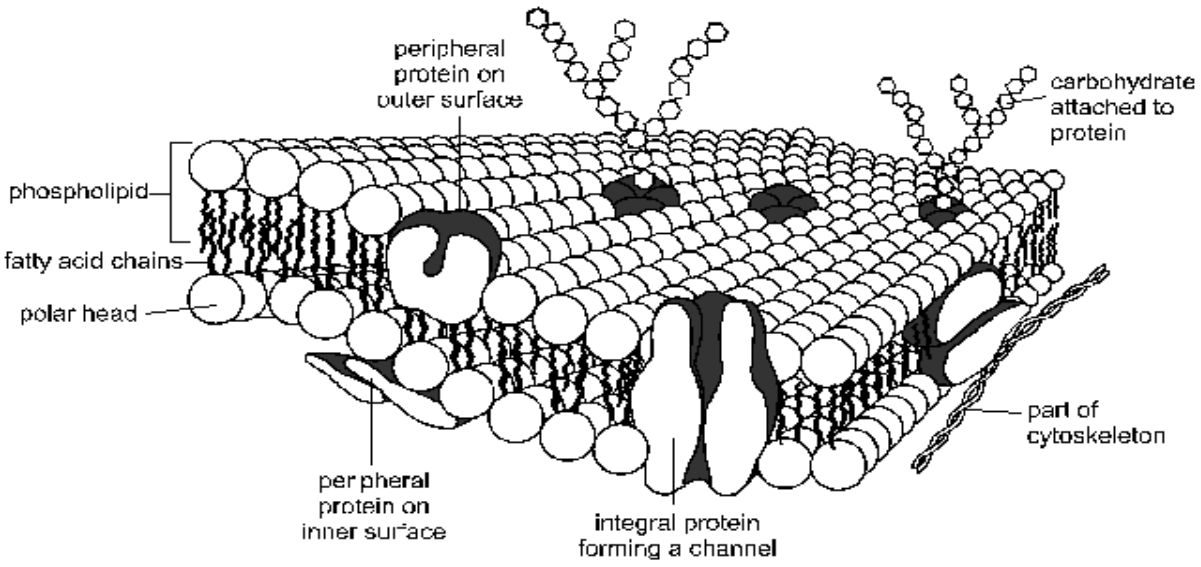


Figure 15: *schematic representation of cell membrane.*

3.1.3 Action potential and conduction

An action potential is an electrical signal similar to the electrical signals in electronic

devices. But whereas an electrical signal in an electronic device occurs because electrons move along a wire, an electrical signal in a neuron occurs because ions move across the neuronal membrane. Ions move through ion channels that open and close due to the presence of neurotransmitter. When the concentration of ions on the inside of the neuron changes, the electrical property of the membrane itself changes. When this depolarization reaches a point of no return called a threshold, a large electrical signal is generated which is called an *action potentials*. Voltage gate ion channels are very important in the generation of an action potential (Purves et al., 2008). The action potential can be divided into six phases (Figure 16):

1)Resting phase: during which only the leaky potassium channels are open establishing the resting potential.

2)Rising phase: the increasing positive shift in membrane potential is driven by the opening of voltage-gated Na+ channels and the entry of Na+ into the neuron. This influx of sodium current depolarizes the membrane voltage.

3) Overshoot phase: it is when the membrane potential is at its most positive state. At this moment two physiological processes are occurring. First the voltage gated sodium channels that initially activated during the rising phase begin to close. As a result, sodium conductance starts to decline. Second potassium channels begin to open driving the membrane potential back toward the equilibrium potential for K+. These gated potassium channels differ from leaky potassium channels in that they are normally closed at resting potential but open in response to depolarization.

4) Repolarization: in the repolarizing phase the membrane potential is rapidly returning to the resting potential. During the falling phase activation of the voltage gated potassium channels is at a maximum, and the number of open sodium channels is

dramatically reduced.

5)Hyperpolarization: at this stage the action potential repolarizes beyond the resting membrane voltage. The undershoot occur because most of voltage gated potassium channels are still open, such that total potassium conductance of the neuron is greater than when the membrane is at rest.

6)Recovery phase: the membrane potentials returns to the original steady state resting potential. This occur as the delayed potassium channels that were opened during the action potential now close. The membrane potential is now determined by the other channels normally open at the resting potential.

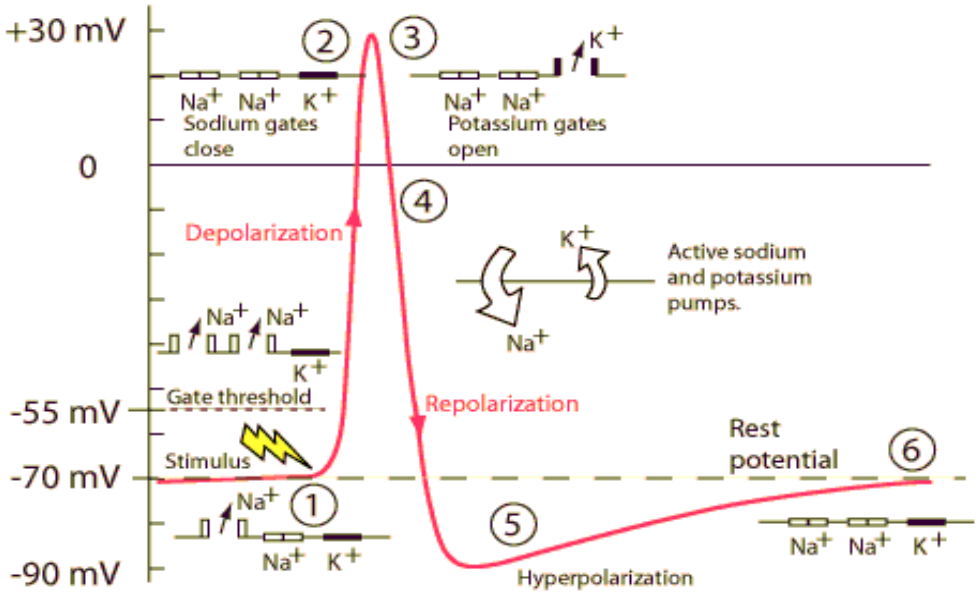


Figure 16: *Different phases of the neuronal action potential are emphasized in this figure. 1, resting state; 2, depolarization to threshold and beyond; 3,peak of the action potential; 4, repolarization; and 5, hyperpolarization,6 recovery phase (adapted from* (Purves et al., 2008).

An action potential travels along the axon quickly, moving at rates up to 150 meters per second. The propagation conduction ends at the axon terminals. Axon terminals are where neurotransmission begins.

3.1.4 Neurotransmission (refer to Kandel, et al., 2013)**:**

Communication between two neurons begins when an electrical impulse called an action potential travels along the axon of a presynaptic neuron toward the axon terminal. The junction between an axon and the next cell with which it communicates is called the synapse and it is achieved by the process of neurotransmission. The part of the synapse that is on the side of the axon is called the presynaptic terminal; that part on the side of the adjacent cell is called the postsynaptic terminal. When the action potential reaches the synaptic button, it causes membranous sacs, called vesicles, to release its contents into the synaptic space. The molecules released from the vesicles are chemicals called *neurotransmitters*. They drift across the synaptic space and bind to special proteins called *receptors* on the postsynaptic neuron. The binding of a neurotransmitter to its receptor can trigger an action potential in the postsynaptic neuron. The electrical signal then moves toward the cell body of the postsynaptic neuron.

Neurotransmitters**:**

The neurotransmitters can have an inhibitory or excitatory effects on the post synaptic neuron. Three major categories of substances that act as neurotransmitters are: (1) amino acids (primarily glutamic acid, GABA, glycine etc.); (2) peptides (vasopressin, neurotensin, etc.); (3) monoamines (norepinephrine, dopamine and serotonin etc.) and acetylcholine. The functions performed by brain neurotransmitters are complex they can be excitatory or inhibitory. In many cases it is the receptor which determines whether the transmitter is excitatory or inhibitory. Receptors can also determine whether a transmitter acts rapidly by direct action on an ion channel or slowly, by a second-messenger system that allows for synaptic plasticity.

The most common neurotransmitters are: Glutamate (Glu): is an excitatory amino acid . The postsynaptic receptors for glutamate include three types of ionotropic receptors,

AMPA, kainate, and NMDA, and eight metabotropic receptors, mGluR1 through mGluR8; Gamma-amino butyric acid (GABA): is an inhibitory amino acid. GABA has an ionotropic receptor, GABAA, that directly gates Cl- channels, and it has a metabotropic receptor, GABAB, that gates K+ and Ca^{2} + channels indirectly; Acetylcholine (Ach): ACh has the nicotinic receptor, which is ionotropic, and the muscarinic receptor, which is metabotropic; catecholamines are a group of transmitters that share the catechol chemical group, and they are all synthesized from the same chemical pathway. Catecholamines are associated with mood, stress, fluid and energy homeostasis, and autonomic function;

Dopamine System: The dopamine system is roughly divided into the three sources. The ventral tegmental area projects to the frontal lobe of the cortex. The substantia nigra projects to the striatum; this system affects fine motor control.

Norepinephrine System: The central norepinephrine system has two main sources, the pons and the medulla. Within the pons, norepinephrine is produced in the locus coeruleus. These areas diffuse projections throughout the brain, and the system affects arousal and mood.

Serotonin(5-HT): Serotonin is produced in the Raphe nuclei. Projections to the spine affect pain while projections to the rest of the brain affect arousal, mood, and the sleep/wake cycle. During the last decade, non invasive brain stimulation (NIBS) has rapidly become a valuable method to investigate the human brain noninvasively. Several studies are investigating the effects of NIBS using pharmacological agents in particularly drugs with a primary mode of action that modulate the major neurotransmitters (Stagg & Nitsche, 2011). In the next chapter the technical characteristics and the mechanisms of action of NIBS will be explained.

3.2 Non invasive brain stimulation

The two most commonly used techniques for non invasive brain stimulation (NIBS)

(Figure 17), transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS) apply different electromagnetic principles to noninvasively influence neural activity (Wagner, Valero-Cabre, & Pascual-Leone, 2007). TMS is a neurostimulation and neuromodulation application of neural tissue, including cerebral cortex, spinal roots, and cranial and peripheral nerves, whereas tCS is a purely neuromodulatory intervention. Both interventions have been applied in the contest of research in neurophysiology and cognitive neuroscience and more recently for potential therapeutic interventions in psychiatry and neurology (Ridding & Rothwell, 2007; J C Rothwell, 1997).

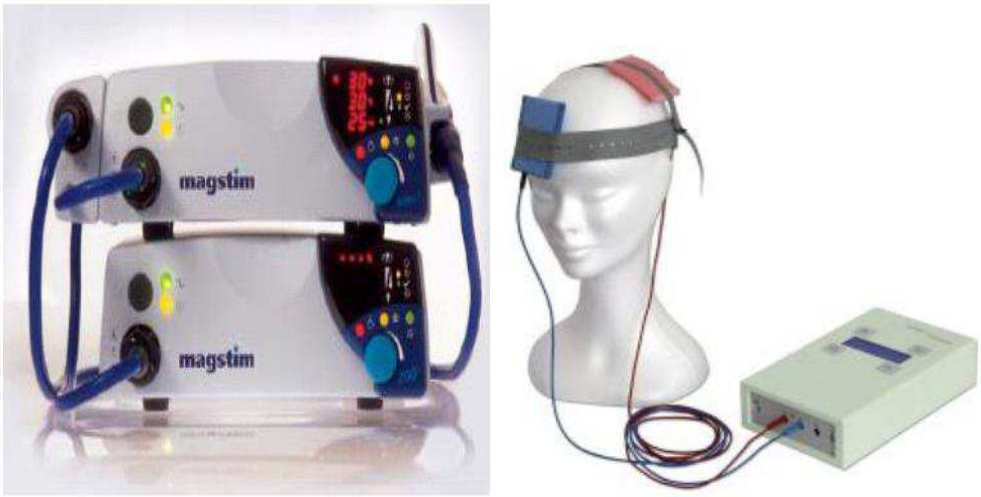


Figure 17:*Ttranscranial magnetic stimulation (TMS) (left) and transcranial current stimulation (tCS) (right).*

3.2.1 Transcranial Magnetic Stimulator (TMS)

The operating mechanism of a TMS stimulator is to create a changing magnetic field that can induce a current in adjacent conductive material (such as brain tissue). The most basic method of generating a magnetic field pulse is to discharge a capacitor across a coil (Barker, et al., 1985). The drive circuitry comprises a power source, a capacitor high

voltage (an energy storage element) and a high-power switch which is precisely controlled by a processor that accepts control input. A very large current flows transiently through the coil and creates a magnetic field (Wassermann, Epstein, & Ziemann, 2008). The magnetic field changes very rapidly and induces electrical currents to flow in the brain (Figure 18). It is possible to control the intensity of the stimuli by changing the intensity of current flowing in the coil. TMS can be applied as single pulses of stimulation, pairs of stimuli separated by variable intervals to the same or different brain areas, or as trains of repetitive stimuli at various frequencies. Therefore the ability of TMS to depolarise neurons can be used to modify intracortical excitability and activate distant cortical, subcortical, and spinal structures along specific connections. However, there are questions about the specific cellular effects of TMS, and further studies are required to clarify the precise mechanisms of action.

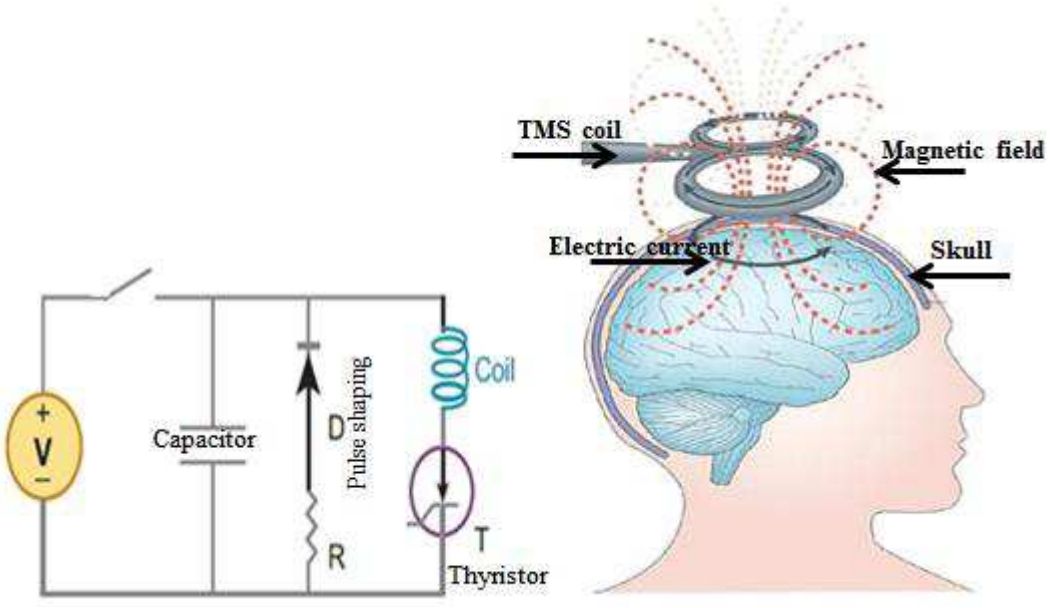


Figure 18: *Left: simplified circuit diagram of a single-pulse magnetic stimulator. Right: schematic representation of the magnetic field generate by TMS.*

The effects of TMS are determine by two fundamental factors such as (Wassermann, 2008):

- Coil shape and orientation.
- Pulse waveform (monophasic or biphasic).

3.2.1.1 Coil shape and positioning

There are several coil with different shapes the most commons are the circular coil and the figure 8 coil (Figure 19).

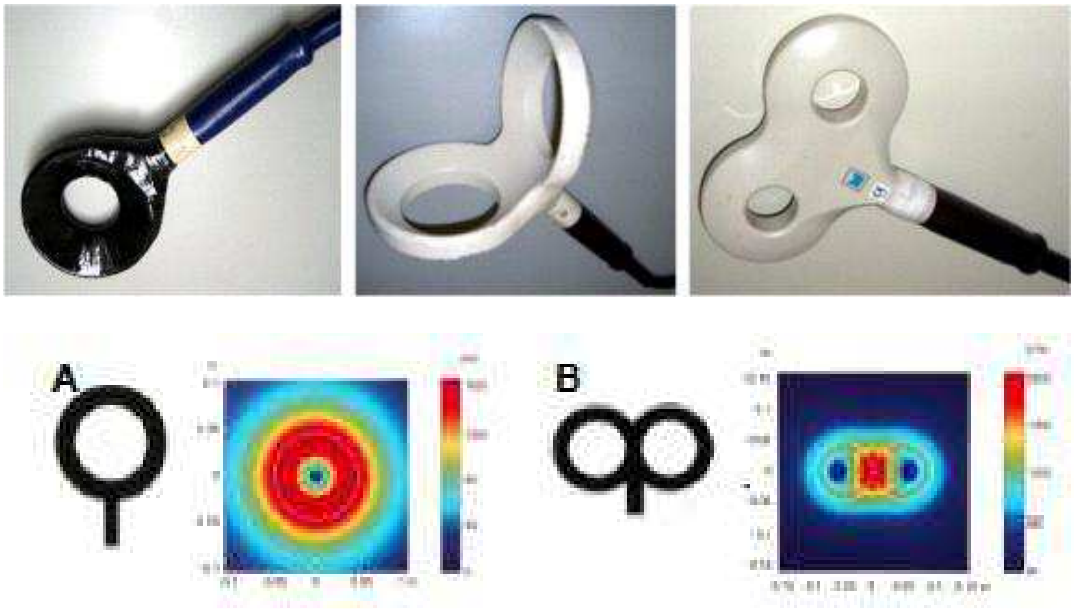


Figure 19: *Top: from left to right: Circular coil, Double cone coil, Figure 8 coil. Bottom: schematic illustration of the magnetic field generated by circulate coil and figure 8 coil.*

Presently, the figure 8 coil is the most frequently use. This type of coil is constitute by two circular coils and such configuration make the maximum of electric current to flow at the junction point (Lu & Ueno, 2009; Ueno, Tashiro, & Harada, 1988). It has been estimated that with the figure 8 coil the depth of stimulation is 2-3 cm below the scalp (Rudiak & Marg, 1994). Other coils have been developed for improve the focality and the penetration, for example in the double cone coil two round coils are bent into a spherical shape and this allow a more deep and focused stimulation . Mathematical approaches for optimizing coil features such as penetration, focality, and efficiency have been proposed (Peterchev et al.,

2012a; Wagner et al., 2007). A crucially important factor is the position of the coil on the scalp in terms of orientation and direction. This is defined by the position of the coil handle in relation to the target of stimulation which determine the current direction. Several studies have also investigated the amplitudes and the latency of MEPs induced in a hand muscle systematically varying the orientation of figure-of-eight coils over the primary motor cortex (Brasil-Neto et al., 1992).Other studies have shown that different orientation of the coil could led to the recruitment of different populations of cortical neurons (Day et al., 1987; Day et al., 1989). For example, posterior–anterior directed current (PA current) preferentially elicits early indirect waves (I-waves) that are due to trans-synaptic activation of pyramidal tract neurons. Antero Posterior current recruits late I-waves and LM current at high stimulus intensity evokes direct-waves(D-wave) (Lazzaro et al., 2001).

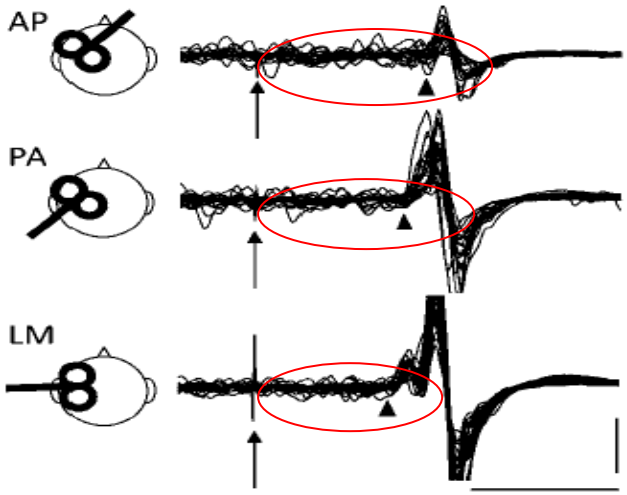


Figure 20: *Arrow indicates the timing of TMS and arrow head indicates the onset of MEPs. Red circles indicates the latencies. PA-directed currents were produced by the figure-of-eight coil held postero laterally at an angle of about 45° to the midline; AP-directed currents were elicited by placing the coil 180° to the PA; LM-directed currents the coil was placed with the handle pointing leftwards for (90° from midsagittal line). The PA-LM latency difference was 1.6 ms , whereas AP-LM was 5.2 ms, compatible with known latency differences between D and I1-wave or I3-waves. adapted from* (Day et al., 1989; Hamada et al., 2013)

3.2.1.2 Pulse waveform (monophasic or biphasic).

There are important technical differences between the two pulse waveforms generated by

the TMS. In the monophasic stimulators the stimulator prevents the coil current from flowing in the reverse direction. Diversely, in the biphasic stimulators there is a second phase of the current. This technical difference has been explored (Sommer et al., 2006). The different pulse waveform has been demonstrated to have a diverse efficacy in define the motor and visual threshold. Interestingly some authors have compared that in the monophasic and biphasic stimulator with a repetitive TMS protocols demonstrating that the monophasic is more effective (Arai et al., 2005).

3.2.1.3 Protocols and applications

TMS is capable of eliciting a motor evoked potential (MEP) which may be recorded by an electromyography. TMS ability to generate an action potential is used to assess the level of corticospinal excitability. Most of our knowledge of the action of TMS on the human cortex comes from studies of the sensory and primary motor cortex (M1). In fact TMS delivered to different levels of the motor system can provide information about the excitability of the motor cortex, the functional integrity of intra-cortical neuronal structures, the conduction along corticospinal as well as the function of nerve roots and peripheral motor pathway to the muscles (Kobayashi & Pascual-Leone, 2003). Stimulation of the motor cortex evokes activity in muscles on the opposite side of the body, which is measured by electrophysiological methods. The activation of cortical descending pathways (Figure 21) by TMS has been suggested to occur predominantly via interneurons in the superficial cortical layers (Di Lazzaro et al., 2007).

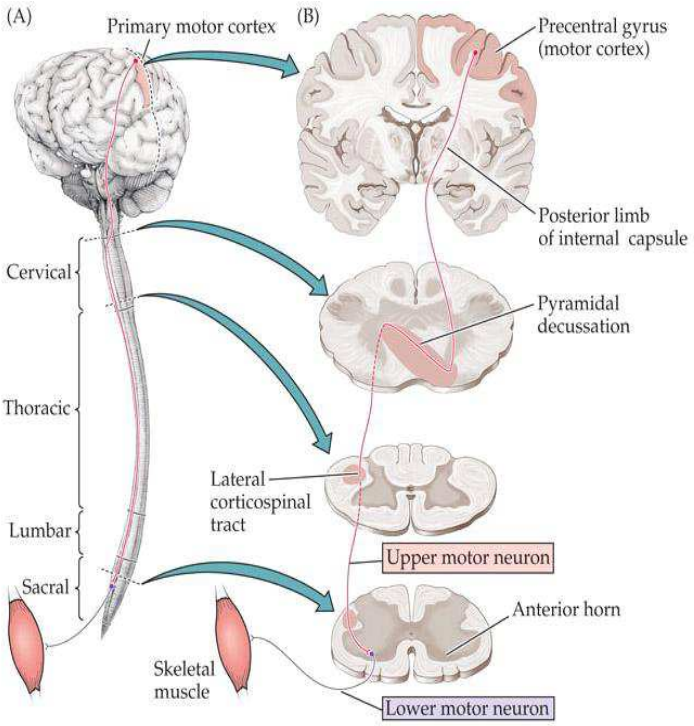


Figure 21: *Schematic illustration of the cortico-spinal tract.*

The next section describes the main TMS protocols investigated :

- Single Pulse
- Paired Pulse
- Repetitive Pulse

3.2.1.4 Single-Pulse TMS

Motor evoked potential (MEP) : The amplitude of the MEP reflects not only the integrity of the corticospinal tract but also the excitability of motor cortex and the conduction along the peripheral motor pathway to the muscles. Patients with dysfunction at any level along the corticospinal pathway may show abnormal MEPs, while the presence of intact MEPs suggests integrity of the pyramidal tract. The reduced amplitude of MEPs is associate with a central motor conduction failure in many cases, but even in healthy people the size and

latency of MEPs shows great inter-individual and intra-individual variability (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000).

Motor Threshold (MT):

When TMS is applied to the motor cortex at appropriate stimulation intensity, motor evoked potentials (MEPs) can be recorded from contralateral extremity muscles. Motor threshold (MT) refers to the lowest TMS intensity necessary to evoke MEPs in the target muscle when single-pulse stimuli are applied to the motor cortex. MT is also been defined as the intensity of TMS that produces an identifiable MEP of 50 μV in at least five out of ten consecutive TMS pulses (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). MT reflects the membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the motor cortex, as well as the excitability of motor neurons in the spinal cord, neuromuscular junctions and muscle. MT provides insights into the efficacy of a chain of synapses from presynaptic cortical neurons to muscles. MT is often increased in diseases that can affect the corticospinal tract, such as multiple sclerosis, stroke, and brain or spinal-cord injury.

Cortical silent period:

When an individual maintains muscle contraction and a single supra threshold TMS pulse is applied to the motor cortex contralateral to the target muscle, the electromyographic activity is arrested for a few hundred milliseconds after the MEP (Figure 22). This period of electromyography suppression is referred to as a silent period (CSP), normally defined as the time from the end of the MEP to the return of voluntary electromyography activity.

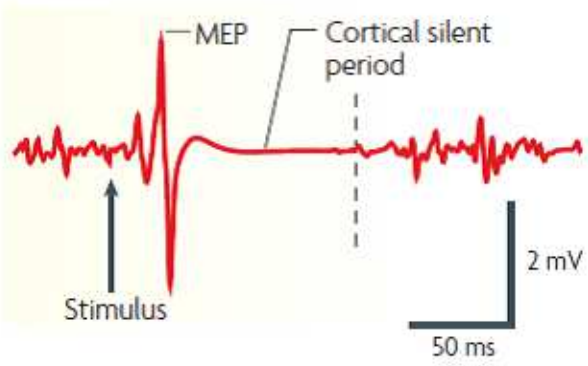


Figure 22: *Schematic illustration of motor evoked potential(MEP) and cortical silent period.*

Assessment of the CPS as a measure of cortical inhibition has provided insights into the pathophysiology of many disorders. The CSP duration provides a measure of cortical inhibitory mechanisms including ($GABA_{B)}$ function, and is influenced by GABAergic medication, dopamine, and ethanol (Ziemann, Hallett, & Cohen, 1998).

3.2.1.5 Paired-pulse TMS

Short interval cortical inhibition (SICI) and Long interval cortical inhibition (LICI):

Variation in pulse intensities and inter-stimulus-intervals (ISIs) also provide different effects. In the experiment of Kujirai et al. (K. Kujirai, 2006) two stimuli are applied over the motor cortex representing the hand area through the same coil. The stimuli are called conditioning and test stimuli and they are applied at specific time intervals which is called inter stimulus intervals (ISI). The intensity of the conditioning stimulus is set below MEP threshold, and the intensity of the supra threshold test stimulus is adjusted to elicit control MEPs with a peak-to-peak amplitude of ~1 mV. The sub threshold conditioning stimulus suppresses the control MEP at ISIs of 1-5 milliseconds (ms). Therefore ISI of a few milliseconds is generally used in the investigation of SICI that seem to reflect GABA ergic interneurons (Di Lazzaro et al., 2000, 2005). An ISI between 7-20 is used in the investigation of intra-cortical facilitation (ICF) that reflect primarily glutamatergic

interneurons (T. Kujirai et al., 1993). Paired-pulse TMS with two supra threshold stimuli given over the motor cortex at long ISIs of 50-200 ms results in inhibition of the test MEP (Valls-Solé, Pascual-Leone, Wassermann, & Hallett, 1992) and this is generally used in the study of LICI. It seems to reflect cortical inhibition mediated through the $GABA_B$ receptors because baclofen, a specific $GABA_BR$ agonist, enhances LICI (McDonnell, Orekhov, & Ziemann, 2006).

It is important to underline that pharmacological studies have demonstrated that SICI and LICI are mediated by $GABA_AR$ and $GABA_BR$ respectively. This suggests that it is possible to study distinct GABAergic inhibitory circuits in human cortex noninvasively by means of different paired-pulse TMS protocols (Wassermann, 2008).

Twin coil studies:

Paired-pulse (pTMS) techniques have been shown to provide measures of intra-cortical facilitation and inhibition as described above well as cortico-cortical interactions, which are important when evaluating changes in system state or functionality (Figure 23). The latter involves protocols to study modulation of human motor cortical excitability by afferent input from other areas of the brain. It consists of two pulses delivered in sequence and is mostly used in the study of inhibitory interactions of motor and premotor cortices. Paired pulses are delivered by two coils located in two different areas, which in this case can be referred to as "twin-coil" stimulation. In this protocol the coil delivering the test stimulus is placed over the primary motor cortex and the other coil delivering the conditioning stimulus is placed over the scalp site that should be connected to the motor area. If the conditioning stimulus, which is given prior to the test stimulus over M1, induces a variation in the amplitude of the test MEP a functional connectivity between the two sites with regard to its timing and its direction (facilitatory or inhibitory) might be inferred (Groppa et al., 2012; Rizzo et al., 2009).

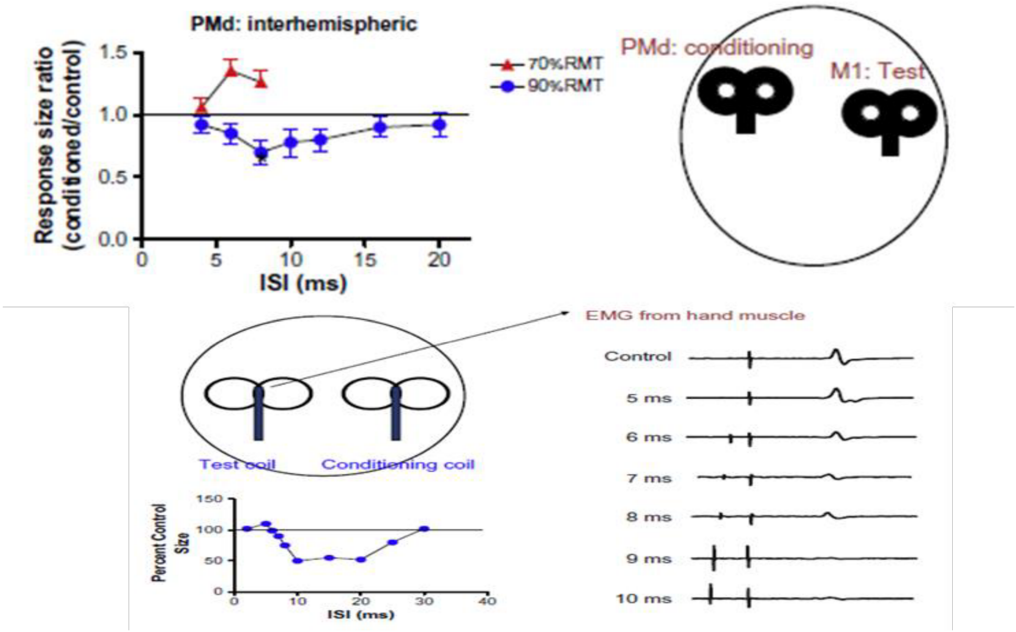


Figure 23: *Inter-hemispheric interaction between PMd and M1 investigated with the twin coil method. Bottom interhemispheric inhibition between the motor cortex hand areas investigated with the twin coil method (adapted from* (Rothwell, 2011).

3.2.1.6 Repetitive stimulation (rTMS):

It refers to the application of regularly repeated stimuli to a single scalp position. In the literature, stimulation with a frequency higher than 1Hz is referred to as "high-frequency rTMS", whereas stimulation with a frequency of less than 1Hz is referred to as "low-frequency rTMS" (Wassermann, 2008). rTMS approach can be used to study adaptive plasticity-like changes in healthy subject. Repetitive rTMS can produce an effect on the excitability of a stimulated area for a period that lasts beyond the duration of the TMS application, depending on the stimulation parameters and inter-individual variability (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000a, 2000b).

New rTMS approaches have been developed which involve the application of high frequency bursts of stimuli at theta frequencies, so called theta burst stimulation (TBS). Continuous (cTBS) and intermittent (iTBS) theta burst stimulation are two such protocols (Figure 24). The stimulus intensity required for TBS (80% of active motor threshold) is lower than that for other rTMS protocols (Huang, Edwards, Rounis, Bhatia, & Rothwell,

2005). The temporal pattern in which these bursts are applied play an important role on the stimulation effects. It has been shown that cTBS tends to depress excitability of the primary motor cortex whereas iTBS has the opposite effect (Huang, et al., 2005). The mechanisms of the modulation of cortical excitability beyond the duration of the rTMS train are still unclear. Long-term potentiation and depression of cortical synapses or closely related neuronal mechanisms have been suggested as possible mechanisms to explain the effect of high and low-frequency rTMS, respectively.

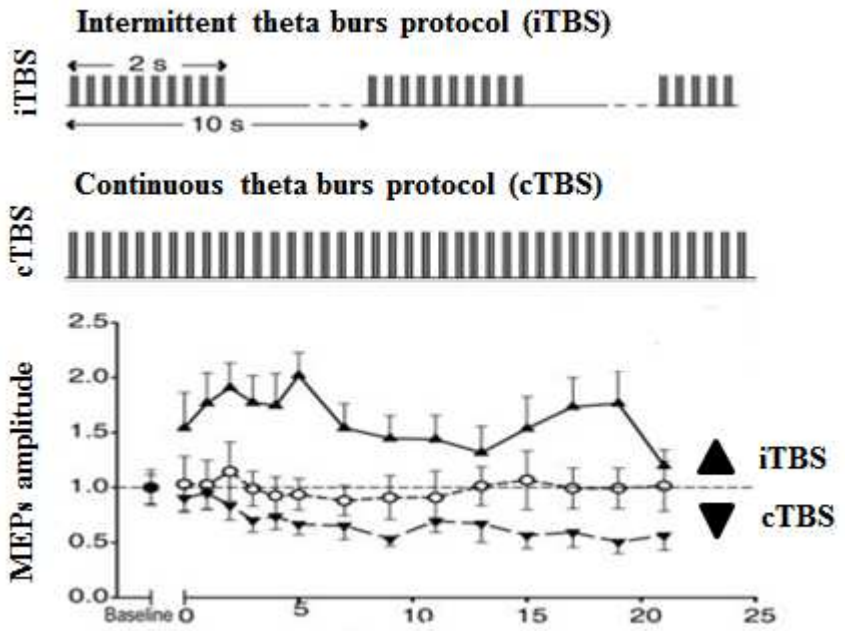


Figure 24: *Top: intermittent (iTBS) and continuous (cTBS) theta burst protocol. Bottom: Distinct effects of the two protocols on cortical excitability assessed by the amplitude of motor evoked potentials(MEPs). iTBS increase MEPs amplitude and cTBS decrease MEPs amplitude (adapted from* (Huang et al., 2005).

3.2.2 Transcranial Electrical Stimulator components

The operating mechanism of tCS is more simple than TMS: a battery source is placed in series with the scalp electrodes and a potentiometer to adjust for constant current. Different types of electrodes exist and they may vary for material, shape and dimension (Peterchev et al., 2012a).

Figure 25: *Transcranial current stimulation (tCS) representing a classic set up of electrodes on the scalp.*

Transcranial current stimulation (tCS) includes transcranial direct current stimulation (tDCS), high- definition tDCS, transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) (Figure 26)(Peterchev et al., 2012a).

In tCS, scalp surface electrodes apply low amplitude currents through the scalp and these currents are applied from few seconds to several minutes (Figure 25). This results in an electric field (measured in volt/meter or related units) and a current density (measured in ampere/meter^2 or related units) generated in the head (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Since tDCS induces changes in polarisation of stimulated brain tissue, the position of the active and reference electrode is critical (Miranda, Lomarev, & Hallett, 2006). It is important to know that the electric field and current density field direction and magnitude vary throughout the head as a function of tissue geometry and impedance. During the stimulation the electric and current density fields also vary as a function of the current outputted by the waveform generator and the dispersive properties of the tissues. Summarizing, the induced modifications in the membrane polarity depend on the parameters like current density, duration and orientation of the electrodes. Recent advances in computational models describe electric current flow by a spatial distribution of vectors (Bikson, Rahman, & Datta, 2012). Modern transcranial electric stimulators typically have

current-controlled output, meaning that the electric current is controlled to follow the waveform characteristics programmed in the device. In the case of voltage-controlled devices, the current injected into the scalp and the current density depends on the impedance between the electrodes and skin. As a result, the electric/current density field waveform in the body may not follow the device-controlled voltage waveform and it may vary widely over time and across subjects (Peterchev et al., 2012b). It therefore follows that an urgent question that needs to be asked is how the current is distributed in the brain during tDCS. To answer this question mathematical models that use information from magnetic resonance imaging (MRI), have been developed to understand the distribution of the electric field in the brain (Datta, Truong, Minhas, Parra, & Bikson, 2012a). These modelling approaches showed that the effects of administering a current in the brain using a particular configuration of the electrodes are the result of many factors such as the spatial distribution of the electric field induced in the gray matter (GM) and white matter (WM), the orientation of the electric field relative to the neurons and many other factors (Miranda, Mekonnen, Salvador, & Ruffini, 2013).

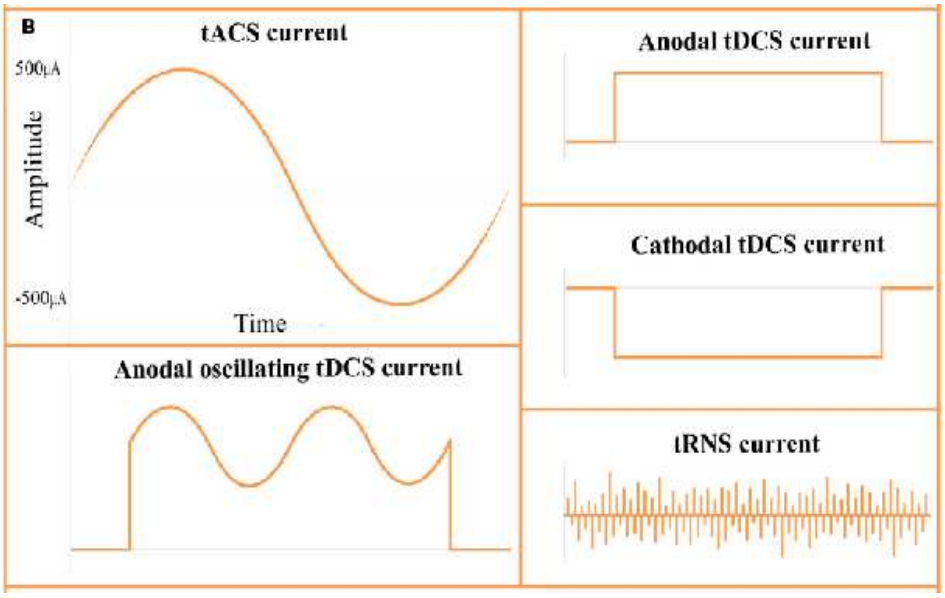


Figure 26: *schematic classification by waveform of transcranial electric current stimulation.(adapted from (Tavakoli & Yun, 2017)*

The next section describe two of these transcranial electric current techniques and the effects of these techniques on the neuronal dynamics.

3.2.2.1 The effects of tDCS on brain physiology

tDCS was the first tCS to be systematically studied. tDCS using weak current, unlike TMS is not able to discharge resting axons to produce action potentials. It can be used to modulate the membrane potential of neurons and modifies spontaneous neuronal activity by a tonic depolarization or hyperpolarization of resting membrane potential (Nitsche et al., 2008; Paulus, 2011). In several studies tDCS has been combined with TMS to investigate modification of cortical excitability by measuring MEPs (Nitsche & Paulus, 2000; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). Generally if the anode is placed above the motor cortex, after DC stimulation , single pulse TMS (sTMS) will result in a larger motor evoked potential (MEP). If the cathode is placed at the motor cortex, MEP size will be reduced. Several studies have been performed in humans in order to understand the physiological mechanisms of tDCS. It has been shown that the effects on the MEP can be modified, prolonged or even reversed by drugs acting on the central nervous system (for review see (Stagg & Nitsche, 2011). Nonetheless, during the last decade a growing body of experimental work have extensively explored the effects of tDCS on brain areas other than the primary motor cortex with encouraging results. tDCS technique has been used to alter cognitive processes. It should be noted that, unlike TMS, the temporal resolution of tDCS is limited, in that the stimulation cannot be time-locked with a relevant stimulus. However the primary mechanism is thought to be a modulation of resting membrane potential affecting spontaneous cortical activity by weak constant current. These studies have demonstrated significant effects of tDCS on cognitive processes as assessed by a variety of cognitive tasks not only in healthy participants but also in clinical populations (Vallar & Bolognini, 2011). As a consequence there has been

growing interest to use tDCS as a safe and relatively low-cost technique for neurological and neuropsychological rehabilitation with variable results (Cappon, Jahanshahi, & Bisiacchi, 2016). Importantly, high variability in the reported effects of tDCS have been demonstrated and it seems to limit the efficacy of this technique (Horvath, Forte, & Carter, 2015; Jacobson, Koslowsky, & Lavidor, 2011; Wiethoff, Hamada, & Rothwell, 2014).

3.2.3 Transcranial alternating stimulation (tACS)

tACS is a newly developed method of tCS. In contrast to tDCS that uses direct current (DC), tACS allows delivery of alternating current at different frequencies. tACS has been used to manipulate ongoing brain oscillations in a controllable way. Previously, rTMS has been proposed as a technique able to interact and to test the causal role of brain oscillations for cognition (Thut, Miniussi, & Gross, 2012; Thut, Schyns, & Gross, 2011b). On the other hand, as depicted in Figure 27, repetitive bursts span a large-scale range of frequencies while tACS is likely to entrain brain oscillations in a selective manner, since the sinusoidal currents are confined to only one frequency (Figure 27). tACS might be used to investigate and modulate the neuronal oscillatory dynamics.

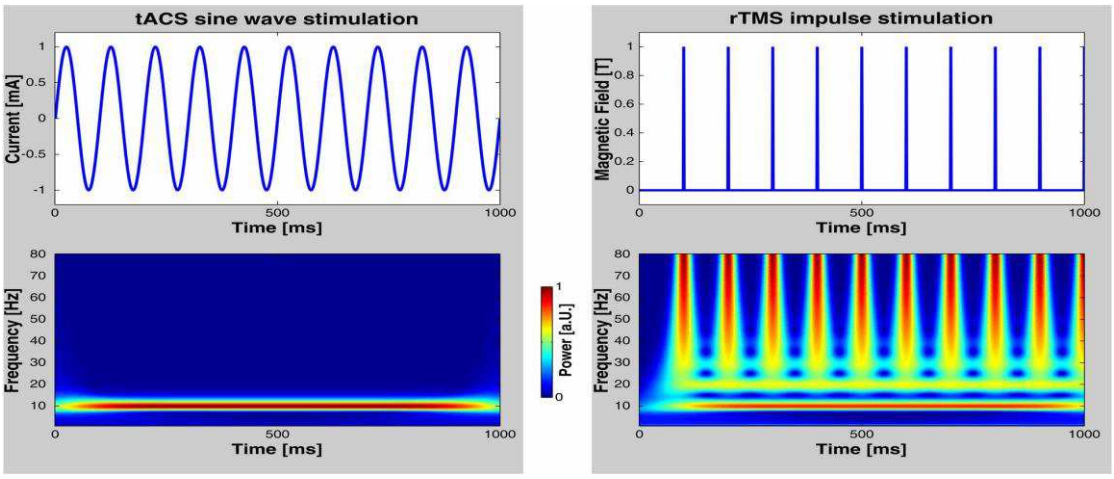


Figure 27: *schematic illustrative model of tACS compare to rTMS on neuronal oscillations showed by a time frequency-wavelet transform (adapted from* (Herrmann et al., 2013).

3.2.4 The effects of tACS on brain physiology

In tACS surface electrodes inject low amplitude alternating current through the scalp and brain to non-invasively induces subthreshold changes in the membrane potentials altering the tendency of stimulating neurons firing in response to a stimulus. The physiological basis of the effects of tACS have been investigated by Fröhlich and McCormick (2010) in an animal study by a simultaneous recording of brain oscillation and multiunit activity during intracranial stimulation of the cortex (Fröhlich & McCormick, 2010a). The authors showed that the application of intracranial sinusoidal current is able to drive the brain oscillations (Figure 28). The first study that applied transcranial alternating current was performed by Ozen and collaborators. They demonstrated for the first time in animal model that weak sinusoidal transcranial current entrains the discharge frequency of widespread cortical neurons (Ozen et al., 2010) for a review see (Reato, Rahman, Bikson, & Parra, 2013). This experimental evidence in animals was used to propose a similar mechanism to explain frequency-specific effects of imperceptible tACS onto the endogenous cortical oscillatory activity in humans. Diverse behavioural effects after applying different tACS frequency give the possibility to show a causal relationship between brain oscillations and different perceptual, motor and cognitive processes (Schutter, 2014).

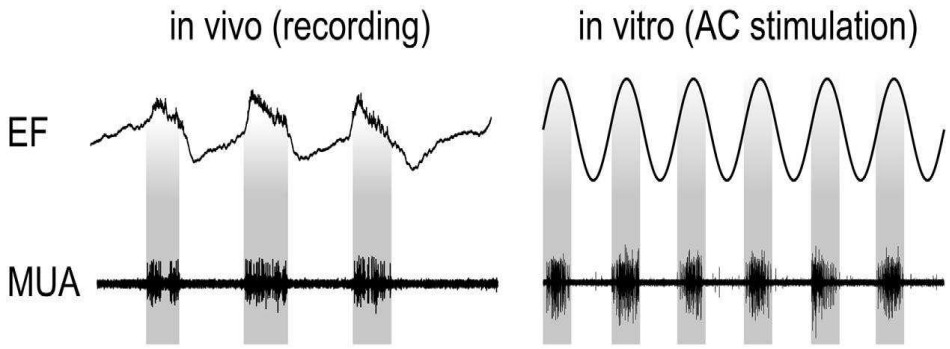


Figure 28: *Left: recordings in ferrets show that spontaneous neuronal activity seen in MUA synchronizes to certain phases of oscillations. Right: applying electrical oscillatory stimulation results in a similar synchronization.(adapted from* (Fröhlich & McCormick, 2010a; Herrmann et al., 2013).

3.2.5 Experimental evidence of tACS in humans

Perceptual domain

The first evidence that tACS can modulate perception in humans have been showed by Kanai and colleagues (2008). The authors delivered an oscillatory current over the occipital cortex under conditions of light or darkness. They showed that the perception of phosphenes increased when the beta frequency range was applied in an illuminated room, whereas the most effective stimulation frequency shifted to the alpha frequency range during testing in darkness. Stimulation with theta or gamma frequencies did not produce any visual phenomena. Feurra and colleagues (2011) delivered tACS at different frequencies over the primary somatosensory cortex and found that stimulation in the alpha and high gamma frequency range elicited tactile sensations in the contralateral hand and a weak effect was also observed with beta stimulation (Feurra, Paulus, Walsh, & Kanai, 2011).

tACS modulation of motor cortex and motor behaviour

As explain earlier for tDCS also for tACS it is possible to measure changes of corticospinal excitability with MEPs after single pulse TMS. Studies using tACS revealed modulation of cortical excitability after tACS intervention (Feurra, et al., 2011; Schutter & Hortensius, 2011). tACS effects on motor behaviour have also been described mainly by adopting a 20 Hz tACS frequency protocol over motor cortex. Previous studies induced movement slowing (Joundi, Jenkinson, Brittain, Aziz, & Brown, 2012; Wach et al., 2013b). Using a go/no-go task, Joundi and collaborators reported an increase in reaction times of voluntary movement during 20 Hz tACS. Wach et al adopting a finger tapping task found movement slowing with 20 Hz tACS, but increased movement variability after 10 Hz stimulation. An innovative approach was used by Pogosyan and colleagues (Pogosyan et al., 2009). They computed the coherence between electromyography (EMG) activity from a finger muscle

and simultaneously applied 20 Hz tACS signal. This resulted in a peak of coherence at 20 Hz briefly before movement onset and led to a slowing of movements. The authors ascribe these findings as a prove that beta oscillations are causally relevant for the execution of movements. An important attempt to discover the cellular mechanisms underlying the 20 Hz tACS effects came from Guerra and colleagues (Guerra et al., 2016). By combining tACS and TMS the authors identified which cortical inter-neuronal populations respond to 20 Hz tACS applied over motor cortex.

tACS modulation of higher cognitive processes

A recent meta-analysis quantify the effects on cognition of tACS in healthy participants (Schutter & Wischnewski, 2016). Fluid intelligence frequency-specific modulation was showed by demonstrating shorter solution times for a visuospatial abstract reasoning task during gamma (40 Hz) tACS as compared to other stimulation frequencies (Santarnecchi et al., 2013). Also the application of theta tACS is able to increase working memory capacity and this was correlated to the P300 latency. Moreover it has been demonstrated that low gamma (40 Hz) tACS is able to modulate endogenous attention. The authors explained this effect as an index of the critical role of low gamma in attentional disengagement and reorientation (Hopfinger, Parsons, & Frohlich, 2017). Speech perception can also be modulated using 40 Hz tACS (Rufener, Zaehle, Oechslin, & Meyer, 2016).

Combining tACS and fMRI

A recent approach is to combine tACS with functional magnetic resonance imaging (fMRI) (Alekseichuk, Diers, Paulus, & Antal, 2016; Cabral-Calderin, Williams, Opitz, Dechent, & Wilke, 2016; Cabral-Calderin, Anne Weinrich, et al., 2016; Vosskuhl, Huster, & Herrmann, 2016). Cabral-Calderin and colleagues showed that tACS applied over the occipital cortex did not exert its strongest effect on regions below the electrodes, but mainly on more distant fronto-parietal regions. This effect could be explained by tACS-

induced modulation of functional connectivity between directly stimulated areas and more distant but anatomically and functionally connected regions.

Combining EEG-tACS

Combined tACS-EEG approaches have been used in humans to precisely characterize the neurophysiological basis of the abovementioned tACS-induced effects:

Off line

Combining EEG and tACS Zaehle and collaborators, were able to demonstrate for the first time that alpha band power in the offline EEG was enhanced after tACS, but not after sham stimulation (Zaehle, Rach, & Herrmann, 2010) . There is also evidence that increases in alpha power after intermittent tACS are independent of the phase in which alpha tACS was applied suggesting that the power enhancement after stimulation reflects synaptic plasticity changes rather than entrainment (Vossen, Gross, & Thut, 2014a).

On line

Being an electric stimulation, tACS interferes with EEG recording. Although the methodological difficulties, attempts to remove tACS-induced artefact have been made recently (Helfrich et al., 2014a; Neuling et al., 2015; Vossen et al., 2014a). Even so, to measure the tACS after effects EEG had to be recorded offline stimulation in almost all studies (Veniero, Vossen, Gross, & Thut, 2015). Adopting a 10 Hz tACS protocol, previous reports demonstrated a specific increment in EEG power spectral density (PSD) in the adjacent (8, 13) Hz band (i.e., alpha-band) during and after stimulation (Figure 29), (Helfrich et al., 2014a).

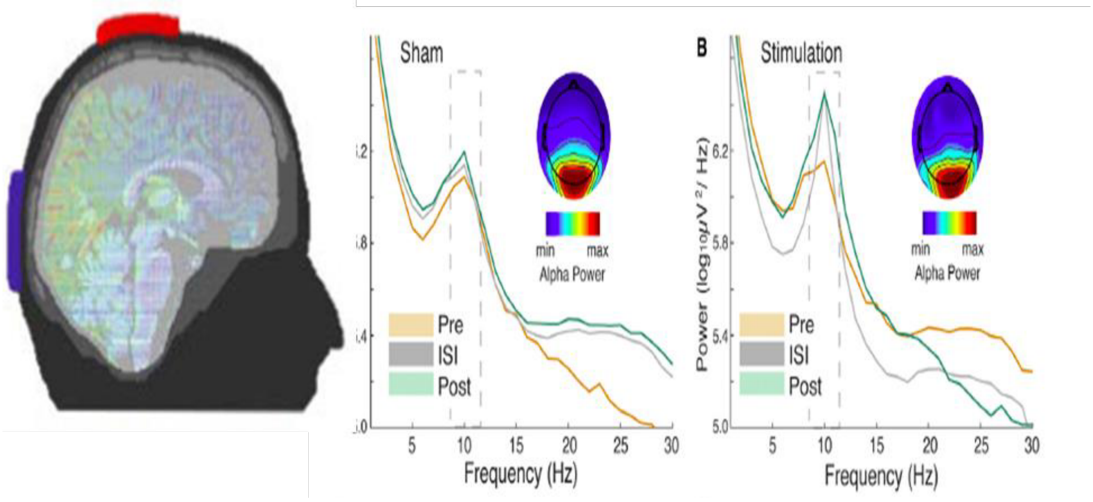


Figure 29: *Left: electrodes montage. Right: applying transcranial alternating stimulation at 10 Hz results in enhancement of alpha band oscillations.(adapted from* (Helfrich et al., 2014b).

Apart from the alpha-band, a recent review highlighted that at present there is scarce evidence of direct tACS-induced modulation of other brain rhythms (Veniero et al., 2015). Moreover, reviewing the literature is apparent that there is still a debate on which is the best way to remove the tACS induced artefact (Noury, Hipp, & Siegel, 2016).

In sum, there is considerable evidence on the capacity of tACS to alter human brain functions both in the perceptual (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008), cognitive (Marshall, Helgadóttir, Mölle, & Born, 2006; Santarnecchi et al., 2013) and in the motor domain (Brittain, Probert-Smith, Aziz, & Brown, 2013; Cappon, D'Ostilio, Garraux, Rothwell, & Bisiacchi, 2016; Feurra et al., 2013; Joundi et al., 2012; Pogosyan et al., 2009). This section has attempted to provide a brief summary of the literature relating to the methodology used in this thesis. This chapter began by describing the basic principles of the neurophysiology that is a prerequisite for understanding the mechanisms by which transcranial magnetic stimulation (TMS) and transcranial alternating current stimulation (tACS) interacts with ongoing brain activity. I then described the recent evidence on the ability of tACS to modulate perceptual and cognitive processes in a frequency specific

manner. This possibility to drive intrinsic brain oscillations through the injection of sinusoidal currents is an advantage compare to tDCS and rTMS.

In the chapters that follow, I present studies that I conducted during my PhD. Chapter 4 presents a review of the literature highlighting the limits, the methodological issues and technical aspects of the tDCS in modulating cognition (electrode position and dimension; current intensity; duration of protocol, inclusion of appropriate assessment tools for cognition, optimal timing for administration of tDCS for cognitive rehabilitation). In chapter 5, I investigate the potential of a new emerging technique - tACS. Chapter 5 aimed to investigate the functional role of beta frequency in the automatic motor processes. In chapter 6 by a combined TMS-tACS approach I investigated the neuromodulatory effects of tACS on motor corticospinal excitability. Finally, in chapter 7 I have combined tACS and EEG with the aim to investigate the neuromodulatory effects of tACS on motor cortex neuronal oscillatory dynamics.

4 TRANSCRANIAL CURRENT STIMULATION IN COGNITIVE REHABILITATION

Summary

Non-invasive brain stimulation techniques, including transcranial direct current stimulation (t-DCS) have been used in the rehabilitation of cognitive function in a spectrum of neurological disorders. The present review outlines methodological communalities and differences of t-DCS procedures in neurocognitive rehabilitation. We consider the efficacy of tDCS for the management of specific cognitive deficits in four main neurological disorders by providing a critical analysis of recent studies that have used t-DCS to improve cognition in patients with Parkinson's Disease, Alzheimer's Disease, Hemi-spatial Neglect and Aphasia. The evidence from this innovative approach to cognitive rehabilitation suggests that tDCS can influence cognition. However, the results show a high variability between studies both in terms of the methodological approach adopted and the cognitive functions targeted. The review also focuses both on methodological issues such as technical aspects of the stimulation (electrode position and dimension; current intensity; duration of protocol) and on the inclusion of appropriate assessment tools for cognition. A further aspect considered is the optimal timing for administration of tDCS: before, during or after cognitive rehabilitation. We conclude that the effects is generally short-lasting and did not generalize to everyday functioning. The findings suggest that several methodological issues must be addressed before clinical efficacy can be determined. More studies using common methodology are needed to gain a better understanding of the efficacy of tDCS as a new tool for rehabilitation of cognitive disorders in a range of neurological disorders.

4.1.1 Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) presented a structure for the diagnosis of neurocognitive disorders. It differentiated "mild" and "major" neurocognitive disorders which may be due to diverse aetiologies (Sachdev et

al., 2014). Neurocognitive disorders (NCD) are described by decline from a pre-morbidly reached level of cognitive functioning. The NCD category includes distinct clinical characteristics in which the primary clinical deficit is acquired and is in cognitive function. The prevalence of NCD increases exponentially with age and at the present moment there are no effective pharmacological treatments for these cognitive deficits. Thus, in the context of rapid population aging worldwide, it becomes important to find new strategies to deal with NCD. Specifically, Parkinson's Disease, Alzheimer's Vascular Disease are particularly debilitating conditions with cognitive sequelae which have increased in prevalence over the years and are a burden for society. In the last decades non-invasive brain stimulation (NIBS) techniques have rapidly become an important approach as potential therapeutic tools to improve the outcome of cognitive rehabilitation in patients affected by stroke, neurodegenerative disorders, or psychiatric diseases (Rossini et al., 2015). The two most commonly used techniques for non-invasive brain stimulation (NIBS) are transcranial magnetic stimulation (TMS) (including single pulse TMS, repetitive (rTMS) and theta burst TMS) and transcranial current stimulation (tCS) (including transcranial direct current stimulation (tDCS), high- definition tDCS, transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS; Peterchev et al., 2012). NIBS apply different electromagnetic principles to non-invasively influence neural activity: In tDCS surface electrodes (anode and cathode) inject low amplitude direct current (0.5–2 mA) through the scalp and brain. In early studies tDCS was combined with TMS to investigate modification of primary motor cortex cortical excitability by recording motor evoked potentials (MEPs) (Priori et al., 1998; Nitsche and Paulus, 2000). The mechanisms are not yet clear but presumably the current induces changes in the resting membrane potential of neurons. These changes appear to be polarity specific with anodal depolarization and cathodal hyperpolarization of resting membrane

potential (Nitsche and Paulus, 2000; Nitsche et al., 2003). Some studies have been performed in order to understand the physiological mechanisms and it seems that neuroplastic after-effects are N-methyl-D- aspartate (NMDA) receptor dependent (Liebetanz et al., 2002; Nitsche et al., 2004). In fact, it has been shown that the effects can be modified, prolonged or even reversed by drugs acting on the central nervous system (Stagg and Nitsche, 2011). It is noteworthy that NMDA receptors have been reported to have a critical role in synaptic plasticity and long term potentiation (LTP) affecting learning and memory. However, these studies are in the motor domain and it is still not clear to what extent these findings are transferable to other areas of the brain. Nonetheless, during the last decade a growing body of experimental work have extensively explored the effects of tDCS on brain areas other than the primary motor cortex with encouraging results. These studies have demonstrated significant effects of tDCS on cognitive processes as assessed by a variety of cognitive tasks not only in healthy participants but also in clinical populations. As a consequence, there has been growing interest to use tDCS as a safe and relatively low-cost technique for neurological and neuropsychological rehabilitation as demonstrated by recent reviews of this topic for various cognitive deficits (Fasotti and van Kessel, 2013; Elder and Taylor, 2014; Flöel, 2014; de Aguiar et al., 2015). The present paper intends to review recent evidence of tDCS for neurocognitive rehabilitation. Our first aim is to discuss the key issues that have emerged from the studies that have demonstrated potential therapeutic applications of tDCS in neurocognitive disorders. Four clinical conditions will be considered namely Parkinson's Disease, Alzheimer's Disease, Unilateral Hemispatial Neglect and Aphasia. The second aim is give the reader an illustration of the methodological communalities and differences of the studies published so far. Finally, we propose a framework of factors that should be taken

into account for an increased understanding of the functional role of tDCS in improving symptoms in patients suffering from neurocognitive disorders.

4.1.2 Methods

Searches were conducted using the online database Pubmed and manual searches of references in relevant papers. The review period was from 2000 to 2015. Articles were identified by carrying out a comprehensive review of published research papers that have used tDCS to improve cognition in patients with Parkinson's Disease, Alzheimer's Disease, Unilateral Hemispatial Neglect and Aphasia. Search terms were ((Parkinson's Disease[Title/Abstract]) AND tDCS [Title/Abstract]) AND (cognitive OR memory OR executive functions OR semantic fluency); ((Alzheimer's Disease or Alzheimer [Title/Abstract]) AND tDCS [Title/Abstract]) AND ((rehabilitation OR cognitive OR memory OR working memory OR attention OR cognition)); ((Neglect[Title/Abstract]) AND tDCS OR transcranial direct current[Title/Abstract]) AND (rehabilitation OR visuospatial attention); (Aphasia[Title/Abstract]) AND tDCS OR transcranial direct current [Title/Abstract]) AND (rehabilitation OR language OR anomia). The initial search identified 122 titles and abstracts. The abstracts and full paper were reviewed to eliminate articles according to the following exclusion criteria: (1) review articles (2) papers that did not include patients with a diagnosis of Parkinson's Disease, Alzheimer's Disease Hemi-spatial Neglect or Aphasia (3) studies that did not focus on cognitive abilities (4) the investigation of other non-motor symptoms or other neuropsychiatric symptoms that were not specified in this review. In total 34 articles met our inclusion criteria (see Table 3).

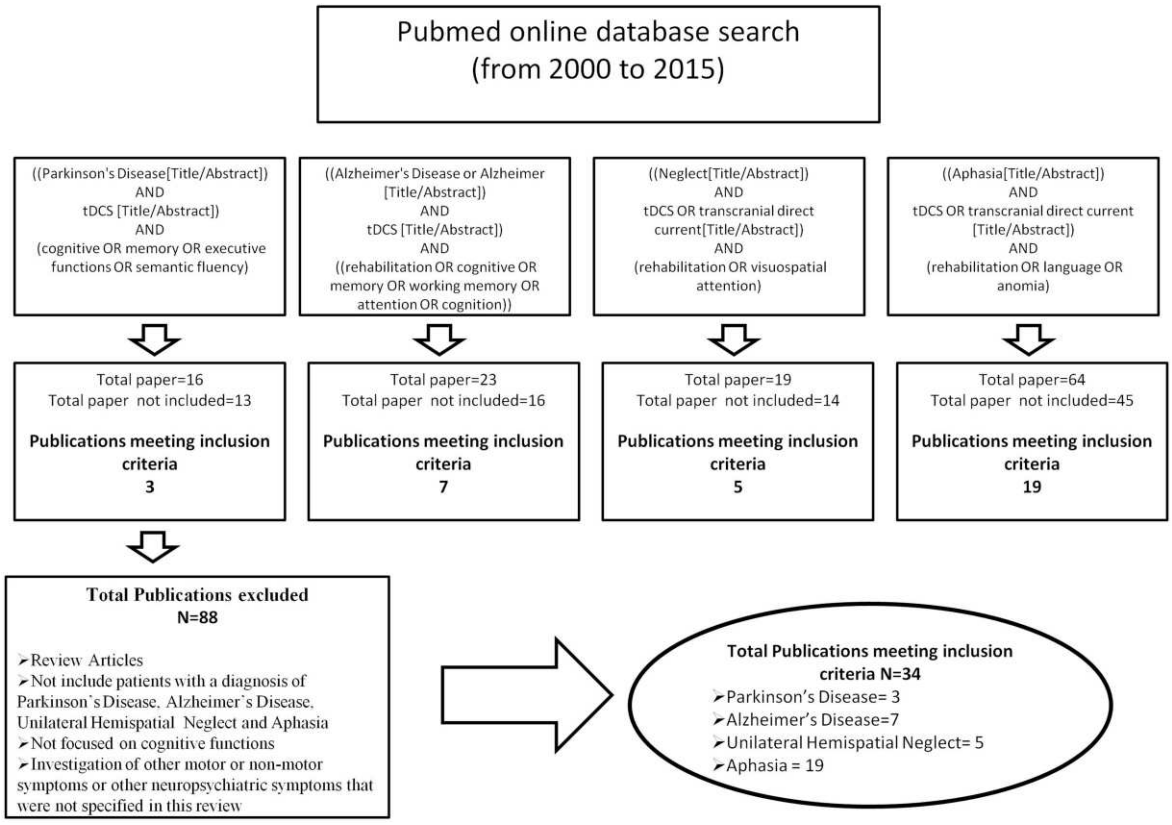


Table 3: *Database key words strategy.*

4.1.3 Application of t-DCS for cognitive rehabilitation

In this section we will review evidence on the use of tDCS for cognitive rehabilitation in patients with Parkinson's Disease, Alzheimer's Disease, Hemispatial Neglect or Aphasia. For each disorder we start with a concise description of the main features of cognitive deficit, followed by a detailed review of the studies. The methodological details of parameters of stimulation used in these studies are presented in Table 4. Patient characteristics, experimental design, cognitive domains targeted, tasks used as outcome measures and main results are summarized in Table 5. In Figures 30-33 are visual representations of the electrode montage which could be useful to compare the studies.

Parkinson's disease (PD)

PD is a chronic and progressive neurodegenerative disorder. PD affects one out of 100 people who are aged older than 60 years in industrialized countries. PD primarily affects dopamine producing neurons in an area of the brain called the substantia nigra pars

compacta. The loss of these specific neurons causes motor symptoms characterized by resting tremor, rigidity, bradykinesia and postural instability. These symptoms are the basis for a diagnosis of PD. Mild Neurocognitive disorders (mNCDs) are also common in PD even in the earliest stages of the disease and significantly impair the quality of life (QoL) of patients (Schrag, Jahanshahi, & Quinn, 2000) and caregivers (Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006). mNCDs in PD include fronto-striatal syndrome due to dopaminergic shortage and include deficits of executive functions, such as planning, mental flexibility and working memory (Dirnberger & Jahanshahi, 2013; Kehagia, Barker, & Robbins, 2010). As the disease progresses, cognitive deficits spread into other cognitive domains and may deteriorate into major Neurocognitive Disorders interfering with independence in everyday activities (Litvan et al., 2011). To date, in patients with idiopathic PD three studies have evaluated the efficacy of tDCS on executive functions. Boggio and colleagues (Boggio et al., 2006) investigated tDCS effects on 18 patients (mean AGE =61 45-71; mean MMSE=24,4) diagnosed idiopathic PD using a three-back working memory task. Patients performed the task during anodal tDCS (A-tDCS) on left dorsolateral prefrontal cortex (L-DLPFC), A-tDCS on motor cortex (M1) and sham. In addition, the authors tested whether the effects depended on the intensity of stimulation; performing a control experiment with different intensities a constant current of 1 mA or 2 mA that was applied for 20 min. The authors found that after a single session of 2 mA A-tDCS over the L-DLPFC patients improved in the accuracy of the 3-back memory task. The other stimulation conditions (sham ,1 mA A- tDCS on L-DLPFC or A-tDCS on M1) were not effective. Their results were recently reinforced by a controlled cross-over, tDCS combined fMRI single session study of Pereira and colleagues. In this study (Pereira et al., 2013) sixteen patients (mean AGE=61.5±.9; mean MMSE=27.7) diagnosed as idiopathic PD were randomized to receive A-tDCS on L-DLPFC (F3) or A-tDCS on L-TPC (P3-T5)

and immediately after performed a verbal fluency task inside the scanner. The authors found an improvement on the phonemic fluency task after a single session A-tDCS over the L-DLPFC. Furthermore, fMRI analysis of connectivity demonstrated that A-tDCS applied over the L-DLPFC produced a greater activation of the specific functional networks engaged by the task compared to A-tDCS over temporal parietal cortex TPC. While these two studies demonstrated that tDCS may improve specific components of executive function, the effects were short-lasting and did not generalize to everyday functioning. A subsequent multicenter study (Doruk et al., 2014) then investigated the efficacy of a multiple sessions protocol in idiopathic PD patients on multiple cognitive domains including executive function, attention, perceptual-motor abilities, learning and memory. Here, 10 consecutive sessions (over two weeks) of A-tDCS over L-DLPFC or A-tDCS over R-DLPFC or sham, were administered by a randomized between subject design on eighteen patients (6 in each group). Cognitive functions were evaluated before, at the end of stimulation sessions and at one month follow-up. It was found A-tDCS over both the L and R-DLPFC compared to sham improved performance only on Trail Making test B at the 1-month follow-up but not on the other outcome measures. Overall, these studies demonstrate that A-tDCS over the prefrontal cortex may be effective for improving executive functions, but it must be emphasized that these studies lack sufficient numbers of patients, statistical power and more importantly transfer of benefits into everyday functioning. Across the studies, there is a general agreement on the parameters of stimulation. While the positions of active electrode A- L-DLPFC (F3) and reference contralateral supraorbital and also the intensity (2mA) and the duration (20min) of stimulation are the same or similar in all studies, it is not clear what the criteria are for selection of the outcome criteria, such as reliability or validity. Furthermore, it is unclear what strategies they have adopted to control the practice effect and what the most sensitive

test to measure tDCS efficacy on cognitive domains may be. In sum, this evidence encourages and warrants further investigation. In future studies shared methodology are necessary to allow comparison across studies and to assert the usefulness of tDCS for cognitive rehabilitation in PD.

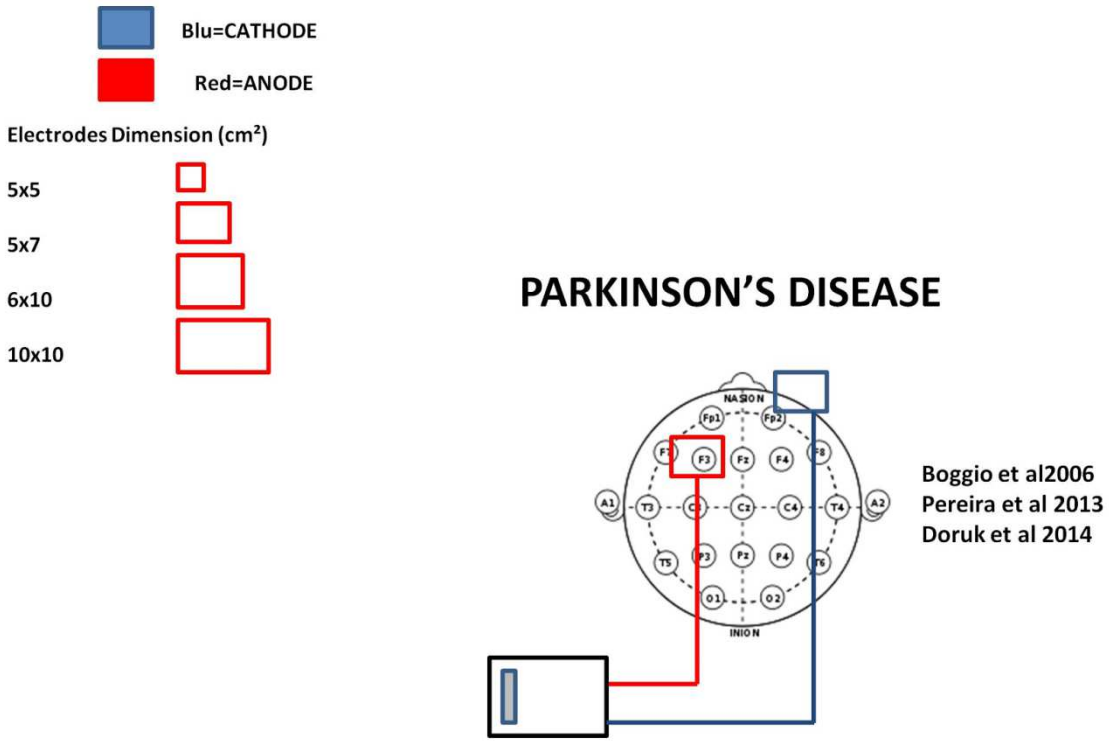


Figure 30: *Legend of electrodes size and polarity and scale representation of tDCS electrodes montage of the reviewed studies with reference to the EEG international 10-20 system. Parkinson's disease studies (Boggio et al., 2006; Doruk et al., 2014; Pereira et al., 2013).*

Table.4 Parameters of stimulation in studies of t-DCS for cognitive rehabilitation in Parkinson's disease, Alzheimer's disease, unilateral spatial neglect or aphasia.

Author & year	Electrodes Position		Electrodes Dimension (cm²)		Intensity (mA)	Current Density (mA/cm²)		Duration (min)	Sessions	Time of stimulation
	'active'	'reference'	'active'	'reference'		'active'	'reference'			
Parkinson's Disease										
Boggio et al. (2006)	1)Anode L-DLPFC 2)AnodeM1	Cathode C.F. Cathode C.F.	35	35	1 2	0,029 0,057	0,029 0,057	20	1	Online partially during WM task
Pereira et al. (2013)	1)Anode L-DLPFC 2)Anode L-TPC	Cathode C.F. Cathode C.F.	35	35	2	0,057	0,057	20	1	Rest
Doruk et al. (2014)	1)Anode L-DLPFC 2)Anode R-DLPFC	Cathode C.F. Cathode C.F.	35	35	2	0,057	0,057	20	10 (2 weeks)	Rest
Alzheimer's Disease										
Ferrucci et al. (2008)	1)Anode L-TPC R-TPC bilaterally 2)Cathode L-TPC R-TPC bilaterally	R-Deltoide	25 25	25	1.5	0,060	0,060	15	1	Rest
Boggio et al. (2009)	1)Anode L-DLPFC 2)Anode L-TC (T7)	Cathode C.F. Cathode C.F.	35	35	2	0,057	0,057	30	1	Online
Boggio et al. (2012)	Anode L-TPC R-TPC bilaterally (T3-T4)	R-Deltoide	35 35	64	2	0,057 0,057	0,031	30	5	Rest
Cotelli et al. (2014)	Anode L-DLPFC	R-Deltoide	25	60	2	0,080	0,033	25	10 (2 weeks)	Online
Khedr et al. (2014)	1)Anode L-DLPFC 2)Cathode L-DLPFC	Cathode C.F. Anode C.F.	24	100	2	0,083	0,010	25	10	Rest
Suemoto et al. (2014)	Anode L-DLPFC	Cathode C.F.	35	35	2	0,057	0,057	20	6 (2weeks)	Rest
Pennolazzi et al. (2014)	Anode L-DLPFC	Cathode C.F.	35	100	2	0,057	0,010	20	10 (2 weeks)	Rest
Unilateral Hemispatial Neglect										
Ko et al. (2008)	Anode R-PPC (P4)	Cathode C.F.	25	25	2	0,080	0,080	20	1	Rest
Sparing et al. (2009)	1)Anode R-PPC (P4) 2) Cathode L- PPC (P3)	Cathode Cz	25	35	1	0,040	0,029	10	1	Rest
Sunwoo et al. (2013)	1)Dual-mode, Anode R- PPC Cathode L- PPC; 2)Single-mode, R Anode R- PPC	1)Cathode C.F.; Anode C.F. 2)Cathode C.F.	25	25	1	0,040	0,040	20	1	Rest
Brem et al. (2014)	Anode R-PPC	Cathode L-PPC	35	35	1	0,029	0,029	20	5	Online

Smit et al. (2015)	Anode R-PPC	Cathode L-PPC	n.a	n.a	2	n.a	n.a	20	5	Rest
Aphasia										
Monti et al. (2008)	1)Anode Broca's area (between T3-Fz and F7-Cz) Cathode Broca's area (between T3-Fz and F7-Cz) 2) Cathode occipital areas (2 cm over the inion)	Cathode R Deltoide Anode R Deltoide Anode R Deltoide	35	35	2	0,057	0,057	10	1	Rest
Baker et al. (2010)	Anode LFC Individually determined (fMRI task)	Cathode R-Deltoide	25	25	1	0,040	0,040	20	5	Online computerized anomia training
Fiori et al. (2011)	Anode L Wernicke's area	Cathode C.F.	35	35	1	0,029	0,029	20	5	Online picture-naming task
Flöel et al. (2011)	1)Anode R-TPC (Talairach) 2)Cathode R-TPC (Talairach)	1)Cathode C.F. 2)Anode C.F.	35	100	1	0,029	0,010	20		Online during the first 20 minutes anomia training
Fridriksson et al. (2011)	Anode LPC Individually determined	Cathode C.F.	25	25	1	0,040	0,040	20	5	Online computerized anomia treatment
Jung et al. (2011)	Cathode R BA 45(between T4-Fz and F8-Cz)	Anode C.F.	35	35	1	0,029	0,029	20	10	Online speech therapy
Kang et al. (2011)	Cathode R- Broca's area	Anode C.F.	25	25	2	0,080	0,080	20	5	Online word-retrieval training
Vines et al. (2011)	Anode R IFG, (2.5 cm posterior to F8)	Cathode C.F.	16	30	1.2	0,075	0,040	20	3	Online Melodic intonation therapy
You et al. (2011)	1)Anode L sTG (CP5) 2)Cathode R sTG (CP6)	1)Cathode C.F. 2)Anode C.F.	35	35	2	0,057	0,057	30	10 (2 weeks)	Online speech and language therapy
Lee et al. (2013)	1)single, Anode L IFG (F7) 2) dual, Anode L IFG (F8) Cathode R IFG	1)Cathode L buccinator muscle 2)Cathode L buccinator muscle Anode R buccinator muscle	25	25	2	0,080	0,080	30	1	Online speech therapy during the last 15 minutes
Polanowska et al. (2013)	Anode L-Broca's area (T3-Fz and F7-Cz)	Cathode C.F.	35	35	1	0,029	0,029	10	15	Rest (followed by 45 min language training)
Rosso et al. (2013)	Cathode R Broca's area (Individually determined ,neuronavigator)	Anode C.F.	35	35	1	0,029	0,029	15	1	Rest
Santos et al. (2013)	Cathode M1of unaffected side (C3/C4)	Anode C.F.	35	35	2	0,057	0,057	20	10	Rest
Volpato et al.	Anode L-Broca's Area (between T3-Fz and F7-Cz)	Cathode C.F.	35	35	2	0,057	0,057	20	10 (2 weeks)	Rest

(2013)										
Marangolo et al. (2013)	1)Anode L Wernicke's area 2)Anode L Broca's area	Cathode C.F.	35	35	1	0,029	0,029	20	5	Ofline training for action naming
Vestito et al. (2014)	LF perilesional site (between T3-Fz and F7-Cz)	Cathode C.F.	25	25	1.5	0,060	0,060	20	10 (2weeks)	Online naming training
Manenti et al. (2015)	Anode L-DLPFC (F3)	Cathode R-DLPFC (F4)	35	35	2	0,057	0,057	25	20	Online verb anomia training
Shaha Basak et al. (2015)	Individualized on the individual response 1)Anode L-IFG(F3) 2)Cathode L-IFG (F3) 3)Anode R-IFG (F4) 4)Cathode R-IFG (F4)	Contralateral Mastoide	25	25	2	0,080	0,080	20	10 (2weeks)	Online picture-naming task
Wu et al. (2015)	Anode L Wernicke's area (between T3-P3 and C3-T5)	Cathode unaffected shoulder	25	25	1.2	0,048	0,048	20	20	Rest

ABBREVIATIONS: BA=Broadmann area; C.F.=contralateral forehead; L=left; R=right; LF=left-frontal DLPFC= dorso lateral prefrontal cortex; IFG=inferior frontal gyrus; mA= milliAmpere ; min=minutes; M1= primary motor cortex; TC= temporal cortex; TPC= temporo-parietal cortex; PPC= posterior parietal cortex; sTG= superior temporal gyrus;

Table. 5 Patient characteristics, experimental design, cognitive domains ,tasks used as outcome measures and main results of studies which used tDCS for cognitive rehabilitation in Parkinson's disease, Alzheimer' disease, unilateral neglect, or aphasia.

Author and year	Sample	Experimental Design	Target Cognitive domain	Neuropsychological measures	Main Results
Parkinson's Disease					
Boggio et al. (2006)	Idiopathic Parkinson N=18	Randomized controlled cross over	Working Memory	Computerized 3 n-back task	A-tDCS (2mA) of left DLPFC improved accuracy as compared with the other conditions.
Pereira et al. (2013)	Idiopathic Parkinson N=16	Randomized controlled cross over	Executive Functions	Computerized verbal fluency task (phonemic fluency, semantic fluency)	A-tDCS L-DLPFC improved performance on the phonemic fluency task as compared L-TPC A-tDCS.
Doruk et al. (2014)	Idiopathic Parkinson N=18	Randomized controlled beetween subject	Abstract Reasoning Executive Functions Selective Attention Visuo-spatial abilities Working Memory	TMT A-B, WCST , DIGSP-BW- FW, HPVOT ,CPM, Stroop test	Both left and right DLPFC A-tDCS groups improved at the 1-month follow-up in TMT-B as compared with sham; no changes in WSCT, PCL, WM, CPM, HVOT,STROOP, and Digit Span
Alzheimer's Disease					
Ferrucci et al. (2008)	AD N=10 (criteria MMSE≥20)	Randomized controlled cross over	Episodic Memory Attention	word recognition task visual attention task	Improvement of accuracy of word recognition memory after A-tDCS; no changes in visual attention.
Boggio et al. (2009)	AD N=10 (criteria 12<MMSE<25)	Randomized controlled cross over	Executive Functions Selective Attention Working Memory	visual recognition, DIGSP-BW- FW, Stroop	Improvement of visual recognition memory after both temporal and prefrontal A-tDCS;no changes in stroop and digit span.
Boggio et al. (2012)	AD N=15 (MMSE>15)	Randomized controlled cross over	Executive Functions Selective Attention Working Memory Global Functioning	Computerized recognition memory task , visual attention task, ,ADAS-cog, MMSE	Improvement of visual recognition memory after A-tDCS persist for 4 weeks; no changes in other measures
Cotelli et al. (2014)	AD N=36 (Mild to moderate AD)	Randomized controlled beetween subject	Attention Episodic Memory Executive Functions Functional status Language Praxia Semantic Memory	Computerized Face-name association task, MMSE, ADL, IADL, Picture naming task, BADA, RBMT, RAVLT, ROCFC, TMT A-B	Both sham and real tDCS led to improvement in FNAT performance; persist 12 weeks only for the placebo group. no changes in other measures.
Khedr et al. (2014)	AD N=34 (criteria 12<MMSE<23)	Randomized controlled beetween subject	Global Functioning Intelligence	MMSE,WAIS-III	both A-tDCS and C-tDCS improved MMSE in contrast to sham ; only C-tDCS improved performance in

					the subscales of WAIS-III.
Suemoto et al. (2014)	AD N=40 (criteria 10<MMSE<20)	Randomized controlled cross over	Global Functioning	MMSE,ADAS-COG	No effects of repetitive A-tDCS L- DLPFC on cognitive measure tested.
Penolazzi et al. (2014)	AD N=1 (MMSE=23)	Single-case controlled cross over	Episodic Memory Executive Functions Working Memory Selective Attention Praxia Visuo-spatial abilities	Computerized word and visual recognition, verbal fluency, CPT, ENB-2	A-tDCS+CT condition had few effects on the cognitive measures; A-tDCS+CT induced a stability of the patient's global cognitive functioning lasting 3 months as compare to sham+CT condition.
Unilateral Hemispatial Neglect					
Ko et al. (2008)	Subacute sroke Neglect N=15	Randomized controlled Cross-over	Neglect Visuo-spatial search Attention	Line bisection, letter and figure cancellation	A-tDCS compare to sham improved both neglect tests performance.
Sparing et al. (2009)	Subacute and chronic stroke Neglect N=10	Randomized controlled Cross-over	Neglect Visuo-spatial search Attention	Computerized line bisection and visual detection tasks	C-tDCS over the unlesioned hemisphere and A-tDCS over lesioned hemisphere reduced symptoms of visuospatial neglect.
Sunwoo et al. (2013)	Chronic stroke N=10	Randomized controlled cross over	Neglect Visuo-spatial search Attention	Line Bisection test ,Star cancellation test	Both dual- and the single-mode tDCS improved performance in the line bisection test as compare to sham. No changes in the star cancelation test.
Brem et al. (2014)	Subacute sroke Neglect N=1	Single-case controlled double-blind	Neglect Visuo-spatial search Attention	TAP,NET,ADL	Biparietal tDCS stimulation, improved covert attention allocation toward left-sided invalid stimuli, line bisection and copying as compared to sham stimulation.
Smit et al. (2015)	Chronic stroke N=5	Double-blind randomized controlled cross-over	Neglect Visuo-spatial search Attention	BIT	No A-tDCS effects were observed for the BIT sub tests.
Aphasia					
Monti et al. (2008)	Chronic stroke Non-fluent aphasia N=8 (Broca'sN=4; GlobalN=4)	Randomized controlled Cross-over	Language (naming abilities)	Computerized overt picture naming task	C-tDCS improved accuracy in picture naming as compare to sham and A-tDCS.
Baker et al. (2010)	Chronic stroke N=10 (Anomic aphasiaN=6; Broca's aphasiaN=4)	Randomized controlled Cross-over	Language (naming abilities)	Computerized picture-word matching task	A-tDCS improved naming accuracy as compared to sham; improvement persist after 1 week.

Fiori et al. (2011)	Chronic stroke N=3 Non-fluent aphasia.	Double-blind randomized controlled cross-over	Language (naming abilities)	Object naming	A-tDCS improved naming accuracy and RTs as compared to sham; improvement persist after 3 weeks in two patients.
Flöel et al. (2011)	Chronic stroke Aphasia (type n.a.) N=12	Randomized controlled Cross-over	Language (naming abilities)	Computerized naming task	Both A-tDCS and C-tDCS improved naming accuracy; effects of A-tDCS persist after 2 weeks.
Fridriksson et al. (2011)	Chronic stroke Fluent aphasia N=8	Randomized controlled Cross-over	Language (naming abilities)	Verbal word-picture matching task	A-tDCS improved naming RTs as compared to sham; improvement persist after 3 weeks.
Jung et al. (2011)	Acute,subacute,chronic stroke Aphasia N=37	Pre test-Post test Design (no sham control group)	Language	Aphasia quotient and Korean Western Aphasia Battery	C-tDCS improved aphasia symphtoms.
Kang et al. (2011)	Chronic stroke Aphasia N=10 Global (n = 3), Broca's (n =4), anomic (=2), tanscortical motor (n = 1)	Double-Blind Randomized controlled Cross-over	LF (naming abilities)	Naming ,picture-word Matching task	C-tDCS improved naming accuracy as compared to sham.
Vines et al. (2011)	Chronic stroke Moderate to severe Non-fluent aphasia N=6	Randomized controlled Cross-over	Language (naming abilities) (verbal fluency)	Verbal fluency tasks, picture description and picture naming.	A-tDCS improved speech fluency as compared to sham.
You et al. (2011)	Subacute stroke Global Aphasia N=21	Randomized controlled beetween subject	Language (Auditory Verbal Comprehension)	AuditoryVerbal Comprehension	C-tDCS improved auditory verbal comprehension as compared to A-tDCS and sham.
Lee et al. (2013)	Chronic stroke Aphasia N=11 (Broca's N=4; Anomic N=5; Transcortical Motor N=2)	Randomized controlled Cross-over	Language (naming abilities)	Picture naming test and picture description.	Both single and dual tDCS condition improved naming accuracy and RTs as compared to sham.
Polanowska et al. (2013)	Subacute stroke Aphasia (moderate to severe) N=37	Randomized, doubleblind, controlled	Language	Boston Diagnostic Aphasia Examination	No differences between A-tDCS and sham group (both improved).
Rosso et al. (2013)	Chronic stroke two groups with (N=11) or without (N=14) infarction in the L-Broca's area. Non-fluent aphasia	Randomizede controlled cross-over	Language (naming abilities)	Computerized picture-naming task	C-tDCS improved picture naming accuracy in the group with lesion in the L- Broca's area as compared to the other group.
Santos et	Chronic stroke	Pre test-Post test Design	Language	Oral language comprehension,	A-tDCS improved comprehension,

al.(2013)	Aphasia N=19 (Broca's N=8;Anomic N=7; Mixed N=4)	(no sham control group)	(oral comprehension, writing, naming and verbal fluency)	copying, dictation, reading, writing, naming and verbal fluency	naming and verbal fluency for animals name; no changes in other outcomes.
Volpato et al. (2013)	Chronic stroke N=8 aphasia (Wernike's N=2; Broca's N=1;AnomicN=2; Transcortical sensory =1; Transcortical Motor N=1; Conduction N=1)	Randomized controlled Cross-over	Language (naming abilities)	Computerized picture naming task	No differences between A-tDCS and sham for object and action naming task.
Marangolo et al (2013)	Chronic stroke N=7 Non-fluent aphasia	Randomized controlled Cross-over	Language (naming abilities)	Computerized action naming task	A-tDCS on Broca's area improved naming accuracy as compared with sham; the effects persist at follow-up 1 week and 4weeks.
Vestito et al. (2014)	Chronic stroke Aphasia N=3	controlled Cross-over	Language (naming abilities)	Computerized picture naming task	A-tDCS improved naming accuracy as compared to sham; improvement persist after 16 weeks.
Manenti et al. (2015)	Chronic stroke non-fluent aphasia N=1	Pre test-Post test Design (no control group)	Language (naming abilities)	Word verb naming	Bi-hemispheric DLPFC tDCS improve verb-naming performances.
Shaha Basak et al. (2015)	Chronic stroke non-fluent aphasia (mild to severe) N=12	Randomized controlled Cross-over	Language (naming abilities)	Computerized picture naming task	C-tDCS improved naming as compared to sham.
Wu et al. (2015)	Subacute stroke N=12	Randomized controlled Cross-over	Language (naming abilities) (comprehension)	Computerized picture naming auditory word-picture identification	A-tDSC improved picture naming and auditory identification as compared with sham.

Randomized Controlled Cross Over= over time, each participant receives an intervention in a random sequence.

Randomized controlled between subject= the various experimental treatments are given to different groups of subjects.

ABBREVIATIONS:

tDCS=transcranial direct current stimulation; A-tDCS=anodal electrode tDCS; C-tDCS=cathodal electrode tDCS; sham=placebo tDCS

ADAS-cog= Alzheimer's Disease Assessment Scale-cognitive subscale; ADL=activities of daily living; BADA= Batteria per l'Analisi dei Deficit Afasici; BIT= behavioural inattention test; CPM=colored progressive matrices; DIGSP-BW- FW=digit span backwards-forwards; ENB-2=Esame Neuropsicologico Breve-2; FNAT=face-naming association task; HPVOT= Hooper Visual Organization test; IADL= Indice di dipendenza nelle attività strumentali della vita quotidiana ; ; MMSE=Mini Mental State Examination; NET= Neglect- test; RAVLT= Rey auditory verbal learning test; RBMT= River mead behavioral memory test; ROCFC= Rey osterrieth Complex figure copy; TAP= test for Attentional Performance; TMT A-B=Trail making test A-B;WCST=Wisconsin card sorting test; WAIS-III= Wechsler Adult Intelligence Scale-Third edition;

Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a progressive disease that arises on a neuropathological background of amyloid plaques (APs) and neurofibrillary tangles (NFTs). AD is the most common form of major NCD, where symptoms gradually progress over a number of years with memory loss and decline of intellectual abilities serious enough to interfere with daily life. This disturbance is related to the degree of brain atrophy in medial temporal lobe involving entorhinal cortex and hippocampus, and also prefrontal areas. Memory disturbances appear early, at first affecting the ability to learn and retrieve information, and later causing impairments in recognition memory and attention. Ferrucci and colleagues 2008 (Ferrucci et al., 2008) in a randomized cross-over study tested ten AD patients (mean AGE= 75.2 years; MMSE=22,7 overlapping 1,8) on recognition memory and visual attention. Patients underwent a single session protocol of A-tDCS or C-tDCS or sham over bilateral temporal parietal areas (two electrodes on the scalp and one reference on deltoid). Before and 30 minutes after stimulation patients performed a word recognition test and a visual attention test. It was found that A-tDCS increased accuracy in word recognition memory, and conversely C-tDCS decreased accuracy. Performance on visual attention did not change. A successive randomized cross over single session study of Boggio and collaborators (Boggio et al., 2008) assessed the efficacy of A-tDCS on recognition memory, working memory and attention in ten AD patients (MMSE between 12-25). Patients participated in three separate sessions to receive A-tDCS over left temporal cortex or A-tDCS over the L-DLPFC or sham. For all conditions, the reference, cathode electrode (35cm2) was placed over the right supraorbital area. Stimulation was delivered during a Visual Recognition Memory task, Stroop, or Digit Span task, with the order randomized across participants. Tasks started 10 min after stimulation onset and lasted until the end of stimulation. Each condition was

separated by at least 48 hours. It was found that both A-tDCS over temporal or prefrontal cortex improved Visual Recognition Memory performance compared to sham. Attentional performance measured by the Stroop was unchanged. Albeit these two studies showed that A-tDCS may positively modulate aspects of memory, the effects were small and without any follow-up measures. To overcome these limitations, three years later, Boggio and colleagues performed a multicenter, cross-over multiple sessions follow-up study. Here, fifteen AD patients underwent five consecutive A-tDCS over left temporal parietal cortex (L-TPC) and right temporal parietal cortex (R-TPC) bilaterally or sham. Visual Recognition Memory, visual attention and general cognition (MMSE) were assessed before, immediately after the end of stimulation sessions and at 4 weeks follow-up. They found that A-tDCS patients improved on Visual Recognition Memory compared to sham. Moreover these effect persisted four weeks after the end of stimulation. There were no changes in visual attention or general cognition. To date, two studies have assessed the combined use of tDCS and cognitive training. Cotelli and colleagues (Cotelli et al., 2014b) evaluated for the first time the impact of tDCS combined with individualized associative memory training (iMT-FNAT) on specific associative memory test and learning and memory, attention, language and perceptual-motor domains. Here, 10 consecutive sessions (over two weeks) of A-tDCS over the L-DLPFC during iMT or A-tDCS over the L-DLPFC during motor training or sham tDCS during iMT; were administered in a randomized between subject design in 36 patients (12 in each group). Neuropsychological assessment and Face-Name Association memory Task (FNAT) were completed at 4 time points (before, 2 weeks after, 3 and 6 months after). An improvement only in selectively trained stimuli induced by iMT irrespective of site by both A-tDCS and sham tDCS group was found. In other words A-tDCS over the L-DLPFC did not have an additive effect on the FNAT computerized training. Moreover, the improvement was

task-stimuli specific and did not generalize to other domains. In a subsequent single case study Penolazzi and colleagues examined the effectiveness of tDCS combined with Individualized Computerized Task (iCT) performance (Penolazzi et al., 2015) . An AD patient of 60 years (MMSE, 23) underwent 10 sessions A-tDCS over the L-DLPFC followed by iCT. iCT (based on the patient's impairment) included verbal working memory task, phonemic fluency task and continuous performance task. Effects on cognitive performance were evaluated by the iCT and by extensive neuropsychological assessment of global cognitive functioning. The authors found iCT combined with anodal stimulation to be better than iCT combined with the sham. Thus, combined 10 daily sessions of A-tDCS over the left prefrontal cortex and iCT slowed down the cognitive decline of the patient more than iCT alone. The differences in the latter two studies (Cotelli et al., 2014a; Penolazzi et al., 2015) may emerge from the key methodological variations between them such as training during stimulation (Cotelli) or training follow stimulation (Penolazzi). Moreover, the authors utilized diverse cognitive training together with different outcome measures to assess stimulation effects. In addition Cotelli et al. used an extra-cephalic reference and Penolazzi et al. a cephalic reference which will have resulted in a different current flow. Recently there have been two studies with a larger number of patients than previous studies. Suemoto and colleagues (Suemoto et al., 2014) examined the efficacy of A-tDCS in forty moderately cognitively impaired AD patients (MMSE 10-20) for apathy and global cognitive functioning. Here, six sessions of A-tDCS on L-DLPFC, versus sham, were administered in a randomized cross-over design. Patients were evaluated at baseline, after the first and the second week of stimulation, and after one week without intervention. The authors found that A-tDCS had no effect on apathy or on global cognitive performance, or the ADAS-Cog sub-items. This study shows that repeated A-tDCS over the left prefrontal cortex in patients with a state of

relatively advanced deterioration is not able to improve their cognitive deficits or apathy. In a multiple session, 2 months follow up study of Khedr and colleagues 2014 (Khedr et al., 2014) 34 patients (mean AGE=69.7 years; mean MMSE=18.1 range 12-23) were tested. Here, ten sessions of A-tDCS or C-tDCS over the L-DLPFC, versus sham, were administered in a randomized between subjects study design. Global cognitive functioning (MMSE) and Intelligence (WAIS-III) were assessed at four time points (baseline; end of the 10 sessions; 1 and 2 months after the end). Furthermore, motor cortical excitability and the P300 event-related potential were assessed at baseline and after the last tDCS session. The authors found that 10 sessions of both A-tDCS or C-tDCS over the L-DLPFC improved MMSE compared to sham with a further increase at one and two months follow-up. Only C-tDCS seemed to have a minor positive effect on a subscale of the WAIS-III. To sum up, there is some evidence from randomized controlled clinical studies showing a beneficial effect of A-tDCS on some specific components of memory. However, it is evident that there is a great deal of methodological heterogeneity across these studies. First, there are diverse stimulation protocols adopted, only two studies used the same location and size of the electrodes (P S Boggio et al., 2008) (Suemoto et al., 2014). Additionally, some studies preferred an extra-cephalic reference to avoid unwelcome interference effects from brain areas underlying the reference electrode. In general, a better definition of stimulation protocols needs to be provided. Second, most of these studies do not consider the fact that cognitively impaired patients can be highly variable in the manifestation of their cognitive problems and in some cases group variability between patients and within a patient from one day to the next can mask the effectiveness of a treatment. Third, by and large most studies did not measure whether the improvement in a specific task has generalized to everyday life. Indeed it is imperative to discriminate between increase in performance on a specific cognitive task

and recovery in more general daily life activities demanding that cognitive function. Further studies should consider the individual characteristics of each patient, better define stimulation parameters and outcome measures and look at translation into everyday cognitive functioning.

Unilateral spatial Neglect

Unilateral spatial neglect is a neurological syndrome that develops following damage to one hemisphere of the brain. It is characterized by a deficit in attention to and awareness of one side of space. It is defined by the inability of a person to process and perceive stimuli on one side of the body or environment, where that inability is not due to a lack of sensation. Unilateral spatial neglect results most commonly from brain injury to the right cerebral hemisphere, causing visual neglect of the left-hand side of space.

Overall, the rational for the studies using tCDS in patients with unilateral neglect is based on Kinsbourne's interhemispheric conflict model. According to this model parietal lobes may exercise interhemispheric inhibition through the connections of the corpus callosum balancing allocation of visuospatial attention toward both hemifields. Brain lesions, as a result of stroke, damage this balance. For this reason A-tDCS is applied to the lesioned hemisphere to increase cortical excitability and the C-tDCS to inhibit the over-activated unlesioned hemisphere. In a double-blind, crossover, controlled experiment Ko and colleagues (Ko et al., 2008) enrolled 15 right-handed subacute stroke patients (mean Age=62.1±8.8 years; mean time post-onset =29–99 days) with left visuospatial neglect due to right-sided cortical and/or subcortical vascular lesions. Patients participated in a single session protocol of A-tDCS over the right parietal cortex (R-PC) (damaged hemisphere). Before and after 'treatment' patients performed a line bisection test and a cancellation test. The authors found an improvement of performance in both tests, indicating a recovery of neglect symptoms, compared to sham. Sparing and colleagues in

a randomized cross-over study (Sparing et al., 2009) tested 10 right-handed patients (mean age=57.3 years; mean time post-onset 2.9-3.5 months) with left visuospatial neglect due to right-sided vascular lesions. Here, a single session of A-tDCS over the right posterior parietal cortex (R-PPC ; damaged hemisphere) or C-tDCS over the left posterior parietal cortex (L-PPC) were conducted. A visual search task and a computerized Line Bisection task were administered before and after tDCS. The authors found that both C-tDCS over the undamaged PPC A-tDCS over the damaged PPC reduced symptoms of visuospatial neglect. More recently, a rather unconventional protocol was pursued by Sunwoo and colleagues (Sunwoo et al., 2013) [14],who used two stimulators and four electrodes on the scalp. A double-blind randomized cross-over study was performed to assess the impact of dual-mode montage with A-tDCS over the R-PPC(P4) and C-tDCS over the L-PPC(P3) concurrently, and to compare single-mode A-tDCS over the R-PPC alone and sham on ten patients with chronic stroke induced neglect (mean age= 62.6 years ± 13.3 mean time post-onset 27.8 ± 60.4 months). Before and after 'treatment' patients performed a line bisection test and cancellation test. It was found that both dual-mode and single-mode tDCS were safe and beneficial for neglect symptoms.

Two studies assessed the impact of multiple sessions of tDCS on Neglect patients. A combined approach was followed by Brem and colleagues 2014 (Brem, Unterburger, Speight, & JÃncke, 2014) ,who combined tDCS and cognitive training. Here, five consecutive sessions of ordinary neglect therapy combined with biparietal A-tDCS over the R-PPC and C-tDCS over the L-PPC, versus sham, were administered in a double-blind, single case cross-over design in a 72-year-old, ambidextrous male patient with stroke of the right posterior cerebral artery. Neuropsychological assessment before and after treatment were evaluated by test for Attentional Performance (TAP) (which includes covert attention, alertness, visual field) and the Neglect- test (NET) (line bisection,

cancelation, copying). Furthermore generalization on activities of daily living (ADL) was also evaluated. It was found that with bilaterally active PPC tDCS improvement was significantly higher than during standard neglect therapy alone or sham. The authors highlighted for the first time the additive effects of tDCS and standard neglect therapy on functional improvement. Importantly the beneficial effects of tDCS was maintained over a follow-up period of 1 week and 3 months. A subsequent study by Smit and colleagues 2015(Smit et al., 2015) evaluated the immediate and long-term effects of multiple sessions of tDCS on five severe chronic hemispatial neglect patients. Here, five consecutive sessions of bilateral A-tDCS over the R-PPC and C-tDCS over the L-PPC, versus sham, were conducted in a randomized double-blind cross-over design. Neuropsychological assessment before and after treatment by Behavioural Attention test (BIT) indicated no symptomatic improvement after bilaterally PPC tDCS stimulation. While these two studies examined the effects of multiple sessions of tDCS, Brem and colleagues tested a single stroke patient in the subacute phase, while Smit and colleagues tested five stroke patients in the chronic phase. In summary, these results are encouraging, but further clinical trials with larger number of patients and follow up are needed. Moreover translation of symptoms amelioration into everyday activities need to be measured.

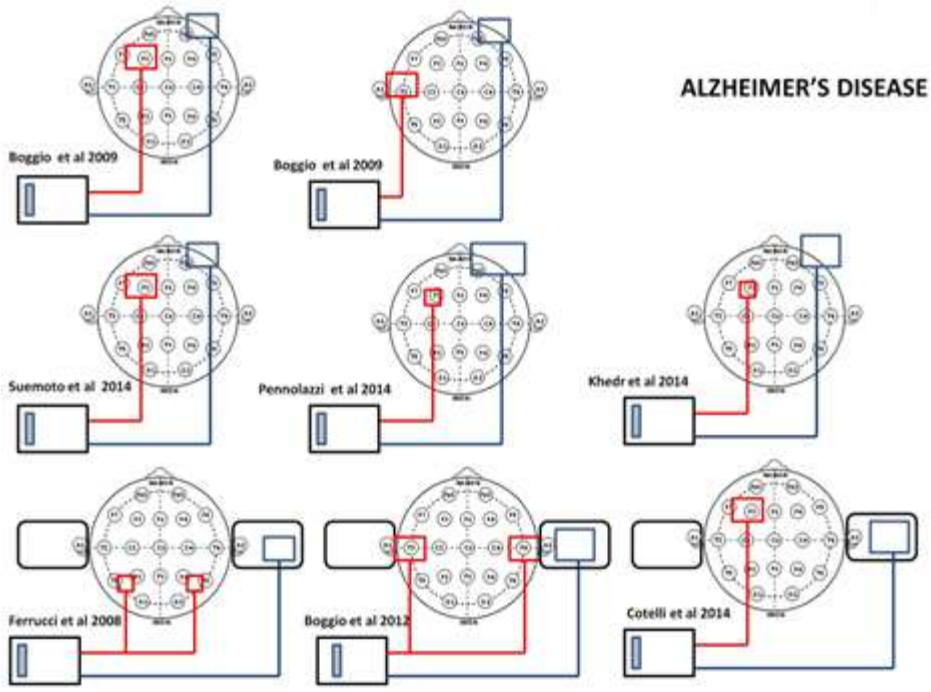


Figure 31: *Scale representation of tDCS electrodes montage of the reviewed studies with reference to the EEG international 10-20 system. Alzheimer's disease (Boggio et al., 2008; Boggio et al., 2012; Cotelli et al., 2014b; Ferrucci et al., 2008; Khedr et al., 2014; Penolazzi et al., 2014; Suemoto et al.)*

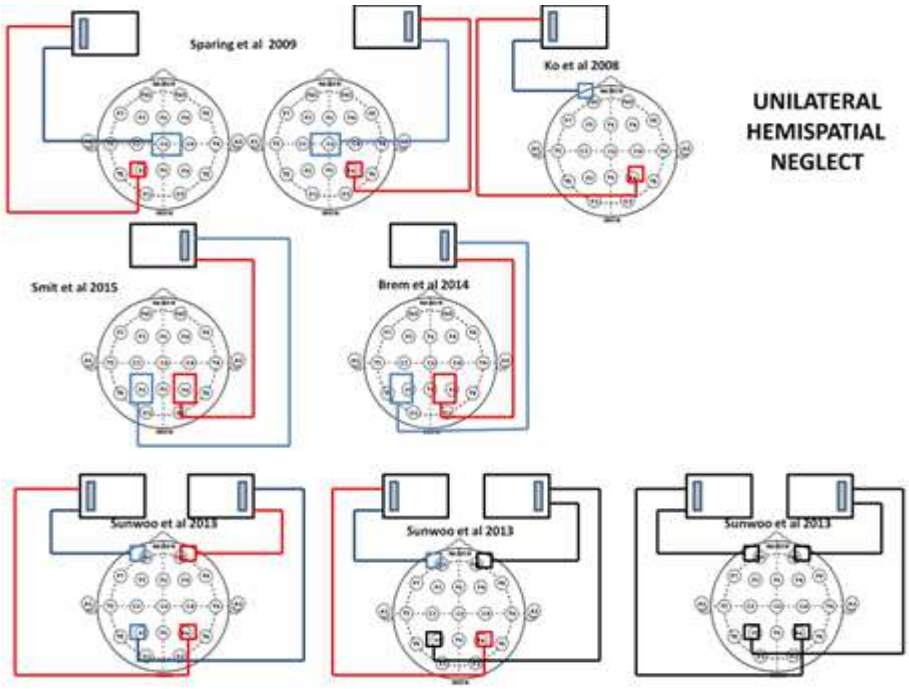


Figure 32: *Scale representation of tDCS electrodes montage of the reviewed studies with reference to the EEG international 10-20 system. unilateral Neglect (Brem et al., 2014; Ko et al., 2008; Smit et al., 2015; Sparing et al., 2009; Sunwoo et al., 2013).*

Aphasia

Aphasia is an impairment of language, affecting the production or comprehension of speech and the ability to read or write. Aphasia is always due to injury to the brain most commonly from a stroke, particularly in older individuals. Aphasia can be so severe as to make communication with the patient almost impossible, or it can be very mild. It may affect mainly a single aspect of language use, such as the ability to retrieve the names of objects, or the ability to put words together into sentences, or the ability to read. Generally multiple aspects of communication are impaired. In this form of aphasia, speech output is severely reduced and is limited mainly to short utterances of less than four words. Vocabulary access is limited and the formation of sounds by individuals with Broca's aphasia is often laborious and clumsy. The person may understand speech relatively well and be able to read, but be limited in writing. Broca's aphasia is often referred to as a 'non fluent aphasia' because of the halting and effortful quality of speech.

In patients who suffer from non-fluent aphasia the studies so far evaluated the immediate effect of tDCS on naming abilities. The first study was conducted by Monti and colleagues in 2008 (Monti et al., 2008), who included eight right-handed chronic non-fluent aphasic patients in a randomized controlled cross-over study. They tested the effect of A-tDCS or C-tDCS over the left Broca's area (damaged hemisphere; crossing point between T3-Fz and F7- Cz) and sham on picture naming task accuracy. An improvement in accuracy after C-tDCS compared to A-tDCS and sham was found. It is worth noting that this study is not in line with the Neglect studies cited above in which A-tDCS was applied over the damaged hemisphere and C-tDCS over the intact hemisphere. Even so these study are difficult to compare because of the differences in the parameters adopted.

Subsequent studies evaluated the effect of A-tDCS over the left damaged hemisphere during naming training in post-stroke non-fluent aphasia patients on naming task

accuracy with mixed evidence. Fiori and colleagues (Fiori et al., 2011) tested three aphasic patients with anomic difficulties using a picture-naming task. In a randomized double-blind cross-over study, they administered five consecutive sessions of A-tDCS over the Wernicke's area (CP5), versus sham applied during intensive anomia training. The authors found a significant improvement in the picture-naming task accuracy. More recently, in eight stroke patients with distinct types of aphasia, Volpato and colleagues (Volpato et al., 2013) examined the effect of A-tDCS on naming abilities. Here, ten consecutive sessions over two weeks of A-tDCS over the L-Broca's area, versus sham were administered in a randomized cross-over design. The authors found no significant differences between A-tDCS and sham on naming abilities. Similarly, in a randomized between subjects study, Polanowska and colleagues (Polanowska et al., 2013) conducted fifteen sessions of A-tDCS over L-Broca's area followed by language training. Patients were assessed by Boston Diagnostic Aphasia Examination before, immediately after treatment and at three months follow up. Again, the authors found no significant differences between A-tDCS and sham groups. In another small sample study, three patients with chronic stroke, in a cross-over design, received naming training during A-tDCS over the left frontal perilesional areas versus sham. Vestito and colleagues (Vestito, Rosellini, Mantero, & Bandini, 2014) found that naming abilities ,as assessed by a computerized naming task, improved in the A-tDCS group compared to the sham group. A rather unconventional protocol was followed by Lee and colleagues who simultaneously used two stimulators. A randomized cross-over study were performed to assess the impact of a dual-mode montage with A-tDCS over the L-IFG (F7) and C-tDCS over the R-IFG (F8) concurrently, compared to single-mode A-tDCS over the L-IFG alone and sham on eleven patients with chronic stroke-induced aphasia. During the last fifteen minutes of tDCS, speech therapy was provided. Before and after treatment,

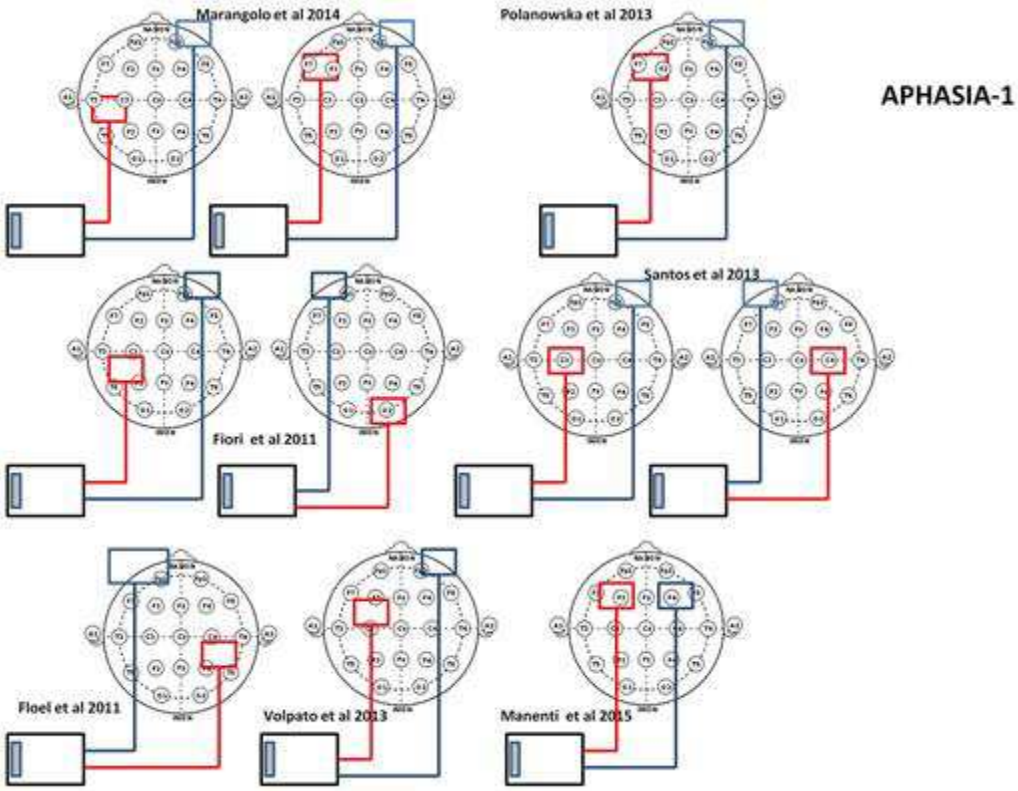
patients performed a picture naming test and a picture description test. It was found that both dual-mode and single-mode tDCS improved naming accuracy and reaction times compared to sham. More recently, Wu and colleagues (Wu et al., 2015) examined twelve sub-acute stroke patients with aphasia using a picture naming task and an auditory picture identification task. Moreover, they measured cortical excitability by electroencephalography (EEG) nonlinear dynamics analysis. In a randomized controlled cross-over study they administered A-tDCS over the L-posterior perisylvian region versus sham and patients received 20 sessions of speech therapy. The authors found an improvement in picture naming and auditory comprehension after A-tDCS compared with sham. Furthermore, EEG analysis indicated that naming improvement correlated with higher activation in the brain language network. Two other studies used an innovative approach to position the electrodes. Baker and colleagues (Baker, Rorden, & Fridriksson, 2010) in a randomized controlled cross-over study tested ten patients in the chronic phase with mild to moderate post stroke non-fluent aphasia. They administered five consecutive sessions of A-tDCS over the left frontal cortex versus sham during computerized anomia training. Each patient performed a naming task inside the scanner. Then fMRI results for each individual was used to place the electrodes. A significant improvement in naming accuracy after A-tDCS compared to sham was reported. The improvement was maintained one week after treatment. In a subsequent study Fridriksson and colleagues (Fridriksson, Richardson, Baker, & Rorden, 2011) tested eight patients with stroke-induced fluent aphasia utilizing the same picture naming task and electrodes placement procedure. Here, five consecutive sessions of A-tDCS versus sham were administered in a randomized controlled cross-over design. Reduced RTs during naming were also found after A-tDCS which was maintained after three weeks.

Some studies assessed the long-term therapeutic benefits of tDCS on naming. In the chronic stage, Marangolo and colleagues (Marangolo, Fiori, Campana, Calpagnano, et al., 2014) included seven patients with stroke-induced non-fluent aphasia in a randomized controlled cross-over study. They administered five consecutive sessions of A-tDCS over the L-Wernicke's area or L-Broca's area versus sham during training for action naming. Training consisted of three groups of video clips representing actions that patients had to name. Naming accuracy was assessed before treatment, immediately after and at one week and two weeks follow-up. The authors found significantly improved accuracy after A-tDCS over the Broca's area compared to Wernicke's area and sham. The effect persisted at four weeks follow-up. This result highlights the functional importance of Broca's area in verb processing. Manenti and colleagues (Manenti et al., 2015) included one chronic stroke patient with non-fluent aphasia in a pre-test post-test design study without sham control. Here, twenty consecutive sessions of bi-hemispheric A-tDCS over the L-DLPFC and C-tDCS on R-DLPFC were followed by individualized verb anomia training. An extensive language evaluation was completed before, after treatment and at 12, 24 and 48 weeks after. The authors found an improvement in verb naming and a decrease in self-perceived difficulties in social situations and improved linguistic abilities suggesting an impact of the treatment on the daily life of the patient. Importantly, the authors asserted that this effect persisted 48 weeks after stimulation. Two studies attempted to improve aphasia symptoms by stimulating the right hemispheric homologue areas. In the chronic stage, Flöel and colleagues (Flöel et al., 2011) included twelve patients with moderate to severe aphasia in a randomized controlled cross-over study. Here, A-tDCS or C-tDCS over the R-temporal parietal cortex (R-TPC) versus sham combined with anomia training were conducted. The authors found that A-tDCS significantly enhanced the overall training effects compared to sham and the effect

persisted after two weeks. Similarly, in a randomized controlled cross-over study, Vines and colleagues (Vines, Norton, & Schlaug, 2011) enrolled six patients with moderate to severe aphasia. They used A-tDCS over the right inferior frontal gyrus (R-IFG) during melodic intonation therapy (MIT) for three consecutive days. They reported that combining A-tDCS with MIT significantly improved verbal fluency compared to sham with MIT. Other studies attempted to restore language abilities by suppressing the right homologue language areas with C-tDCS. In the sub-acute stage, You and collaborators (You et al., 2011) included twenty-one patients with comprehension impairment in a randomized controlled between subjects design. Here, ten sessions of conventional speech therapy were combined with A-tDCS over the left superior temporal gyrus or C-tDCS over the right superior temporal gyrus or sham. It was found that auditory verbal comprehension improved after C-tDCS over the right hemisphere compared to A-tDCS and sham. Similarly, in a double-blind randomized controlled study, Kang and colleagues found that five consecutive sessions of C-tDCS over the R-Broca's area combined with word-retrieval training improved performance in picture-word matching task. Three studies concentrated on factors associated with response to C-tDCS protocol. Jung and colleagues (Jung et al., 2011) included thirty seven stroke patients from acute to chronic in a pre-test post-test design study without sham control group. Here, ten consecutive sessions of C-tDCS over the R-inferior frontal gyrus were administered. The authors assessed the effect of tDCS by the Korean version of Western aphasia Battery. Using regression statistical models it was found recovery after C-tDCS was more in patients with less severe aphasia who had started 'treatment' within the first months after stroke. In a more recent, randomized controlled cross-over study, Rosso and colleagues (Rosso et al., 2014) adopted an innovative fMRI combined tDCS approach looking for inter-individual variability. They found C-tDCS over the R-Brocas's area improved

performance on a computerized picture naming task. More importantly the authors found that improvements in naming after C-tDCS of the R-Broca's area relies on several structural and functional factors. One study assessed the efficacy of an individualized tDCS treatment in stroke-induced non fluent aphasia in chronic patients. Shah Basak and colleagues (Shah-Basak et al., 2015) ingeniously took into account the individual variability in response to tDCS. In the first phase of the study the authors individualized the protocol based on individual responses to the A-tDCS or C-tDCS over the L-IFG or R-IFG. Then in a randomized cross-over study, ten sessions of active tDCS or sham were administered during a picture naming task. Language abilities were assessed before, after treatment, two weeks and two months after. Aphasia symptoms improved after the active tDCS treatment compared to sham and the improvement remained two month after the end of treatment. This study suggests that an individualized protocol may be effective in improving stroke-induced chronic aphasia symptoms overcoming the high variability between patients. An unusual approach was followed by Santos and colleagues (Santos et al., 2013). They included nine teenaged chronic stroke sufferers from non–fluent aphasia in a pre-test post-test design study without sham control group. Here, ten consecutive sessions of A-tDCS over the primary motor cortex (M1) of the healthy hemisphere were administered. Language level was assessed before and immediately after the treatment. They found a significantly improved performance in sentence comprehension, naming and specific animal name category verbal fluency. In sum, there are some randomized controlled evidence that indicated a favorable effect of tDCS in improving language symptoms related to aphasia. Again, there is a great deal of methodological heterogeneity across these studies. Various approaches have been undertaken including the application of A-tDCS over the left damaged hemisphere concomitant to a naming training or to restore naming abilities by suppressing the activation of the right homologue language

areas with C-tDCS. In a rather original fashion, one study took individual differences in response of tDCS into account.



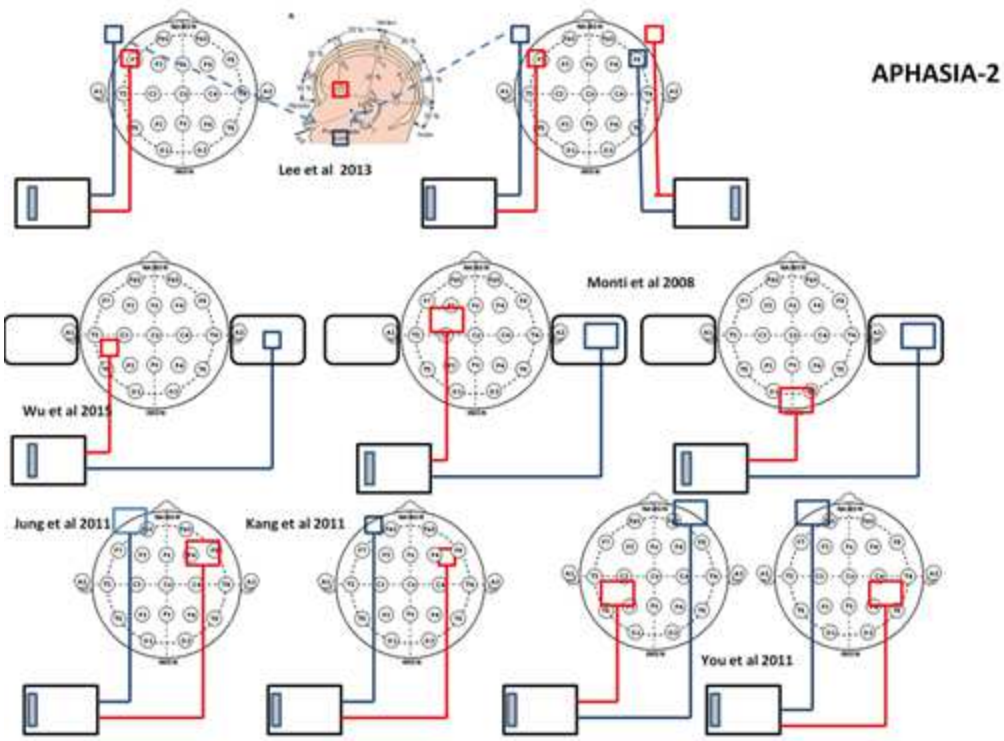


Figure 33: *Scale representation of tDCS electrodes montage of the reviewed studies with reference to the EEG international 10-20 system. Aphasia* (Fiori et al., 2011; Flöel et al., 2011; Jung et al., 2011; Kang et al., 2011; Lee et al., 2013; Manenti et al., 2015; Marangolo, Fiori, Campana, Antonietta Calpagnano, et al., 2014; Monti et al., 2008; Polanowska et al., 2013; Santos et al., 2013; Volpato et al., 2013; Wu et al., 2015; You et al., 2011).

4.1.4 Methodological Issues

Clinical and demographic characteristics of samples

It is important to remember that neurodegeneration or insult or injury to the brain does not affect two people identically. Such individual differences also lead to differences in the evolution of the disease. Even though patients have been diagnosed with the same disorder there are substantial differences between them. In the case of progressive degenerative diseases such as PD and AD, the evolution and progression of the disease is unique in each case and each person responds differently to treatment.

Furthermore, numerous studies have argued that there are some important factors that can affect the evolution of NCD. Cognitive Reserve (CR), for instance, is a factor that would be reasonable to consider in the case of neurodegenerative disorders (Stern, 2002). CR is a term describing the resilience of the brain following the brain damage. CR is defined as the ability to optimize or maximize performance through differential recruitment of brain networks (Scarmeas et al., 2003). It depends on factors such as education, profession, lifestyle and leisure activities which play an important role in determining how many alternative resources are available to be used to compensate for the cognitive deficits. With regards to medical conditions that occur after a brain injury such as unilateral spatial neglect and aphasia there are many points to consider. First, it is almost impossible to find two patients with damage that affects exactly the same part of the brain because of anatomical differences between individuals. Cerebral infarction and hemorrhage may be more or less circumscribed involving diverse brain areas. Second, even if we find two patients with exactly the same injury the two individuals could have a different ability to recover or to compensate. Third, in patients who have suffered a stroke an important aspect to consider is whether patients are treated in the subacute phase (within 6 months) or in the chronic phase. It has been suggested that the brain is more sensitive to reorganization during the months immediately after the stroke. Fourth, it would be important to consider the pre-morbid cognitive state of the participants. Selection of patients for inclusion in the experimental group is an important and sometimes difficult process in this areas of research. Group variability can affect the outcome of a study. It is extremely important to minimize the heterogeneity of patients in order to gain a better understanding of tDCS as a therapeutic technique. Bearing this in mind, there are remarkable differences in the demographic and clinical characteristics of patients undergoing tDCS treatment in the studies examined (see Table 5). For example, regarding

AD in the study of Boggio and colleagues 2009 (Boggio et al., 2008) there is a huge intragroup variability. A patient with an MMSE score of 12 (moderate cognitive impairment) is in the same group as a patient with an MMSE score of 25 (mild cognitive impairment). These patients were comparable for age, respectively 85 and 89, but different for years of education, respectively 4 and 11 years. Suemoto and collegues recruited patients and divided them into two groups with mean ages of 79.4 and 81.6 years; 5 and 4.5 years of education and a MMSE score of 15 and 15.4 (Suemoto et al., 2014); while in the single case study of Penolazzi et al the patient's age was 60 years, with 18 years of education and an MMSE of 23 (Penolazzi et al., 2015). In the study of Khedr and colleague (Khedr et al., 2014) the average age of the three groups of patients recruited was 68.5, 70.7, 67.3 years and MMSE scores of 18.4, 18.8, and 16.9; and years of education was not reported.. Regarding PD, Boggio and colleagues 2006 (Boggio et al., 2006) recruited patients with a score of 36.8 for Experiment 1 and 43 for Experiment 2 on the UPDRS while in the study of Pereira and colleagues (Pereira et al., 2013) patients were recruited with a mean score of 13.3 on the UPDRS. Furthermore, in the study of Boggio et al the average years of education of the patients was 4.7 years for Experiment 1 and 5.3 years for Experiment 2; while in the study of Pereira et al the patients' average schooling was 12.3 years. With regards to unilateral spatial neglect, there are remarkable intragroup differences in the site of damage of the patients. In the studies reviewed in the same experimental group there are patients with damage limited to the basal ganglia, patients with more extensive lesions covering frontal, temporal and parietal lobes or frontal parietal occipital lobes. Another factor on which the patients differed is the duration of illness post onset. Most of the studies recruited patients in the subacute phase within 6 months after stroke (Brem et al., 2014; Ko et al., 2008; Sparing et al., 2009). Only two studies enrolled patients in the chronic phase (Smit et al., 2015;

Sunwoo et al., 2013). In the existing studies, it is often neglected that clinical features of patients may affect the outcome of tDCS. To date, little importance has been given to patient characteristics which could in part explain the variability in the response to the tDCS. Future studies should try to control as much as possible factors that may influence the outcome of therapeutic application of tDCS in cognitive rehabilitation.

tDCS Parameters, electric fields and neuroanatomy

tDCS scalp surface anodal and cathodal electrodes inject low amplitude direct currents (0.5-2 mA) through the head and these currents are applied from few seconds to several minutes. This results in an electric field and a current density generated in the scalp and brain. Generally if the anode is placed above the motor cortex, after DC stimulation , single pulse TMS will result in a larger MEP (Day et al., 1987; J C Rothwell, 1997). If the cathode is placed over the motor cortex, the MEP size will be reduced. Thus, long-lasting and polarity-dependent changes in neural excitability of the human cortex are elicited. This effect is conceivably due to depolarization of somatic membrane potentials by anodal currents and hyperpolarization of soma by cathodal currents, as observed in animal studies (Bindmann, Lippold, & Redfearn, 1964) Several studies have been performed in humans in order to understand the physiological mechanisms of tDCS. It has been shown that the effects on the MEP can be modified, prolonged or even reversed by drugs acting on the central nervous system (Stagg & Nitsche, 2011). Importantly, it seems that neuroplastic after-effects of tDCS are NMDA-receptor dependent (Liebetanz, Nitsche, Tergau, & Paulus, 2002). Moreover, anodal after-effects can be selectively suppressed by both the sodium channel blocker carbamazepine and the calcium channel blocker flunarizine (Nitsche et al., 2003). These studies demonstrated that is possible to measure in humans the effects of direct current application by TMS at the motor cortex. Based upon what is known about the process of MEP production a growing interest for

examining the anodal and cathodal tDCS effects on other brain areas has emerged. It is worth noting that it is absolutely unclear whether it is possible to generalize these processes in the modification of MEPs to other more complex cognitive processes. In spite of this during the last decade a considerable amount of literature has been published on the capacity of tDCS to alter human brain functions over numerous brain areas and in the treatment of a wide range of diseases. This interest has been facilitated by the fact that from a neuroscience point of view, the causal and interventional nature of tDCS is particularly exciting. This exponential growth of published works is somewhat surprising if we consider that the understanding of the basic principles of tDCS have not yet been achieved. Perceiving, remembering, reasoning and language are more complex processes than MEPs. Moreover, many studies are based on the theoretical assumption that placing the anode electrode over the area of interest would enhance precisely the activity of the target region and conversely placing the cathode would decrease the activity, which raises a number of problematic points. One problem with this approach is the low spatial resolution of tDCS. The rationale that putting an electrode on the scalp over a region of the brain results in a precise stimulation of that region, and only the target region is unlikely to be accurate. Indeed the major drawback is that the amount and distribution of current flow fluctuates extensively as a function of individual physiology and anatomy. So investigators who use tDCS are not in a position to make accurate inferences about the operation of a specific brain area. It is not sufficient to only examine the behavioural outcome to ascertain the specific involvement of a brain area and rule out the possible role of another area. It therefore follows that an urgent question that needs to be asked is how the current is distributed in the brain during tDCS. To answer this question recently modern mathematical models that integrate structural resonance magnetic images (MRI), have been developed to understand the distribution of the electric field in the brain (M.

Bikson et al., 2012; Datta, Truong, Minhas, Parra, & Bikson, 2012b). These modelling approaches showed that the effects of administering a current in the brain using a particular configuration of the electrodes are the result of many factors such as the spatial distribution of the electric field induced in the grey matter (GM) and white matter (WM), the orientation of the electric field relative to the neurons and many other factors (Miranda et al., 2013). In light of this complexity, the application of tDCS to neurocognitive disorders should consider the brain morphological heterogeneity of patients. Along these lines it is difficult to conceive that the same stimulation protocols with the same parameters of stimulation may be optimal in different patients. For instance, in the case of degenerative disorders characterized by marked atrophy such as AD it is difficult to conceive that the same dose of tDCS is optimal in two different patients as suggested by Mahdavi and collaborators (Mahdavi, Yavari, Gharibzadeh, & Towhidkhah, 2014). An interesting parallel in this regard is with deep brain stimulation (DBS). DBS is a neurosurgical procedure in which an electrode is implanted in the brain and is controlled by a neuro-stimulator. In DBS the patient's behavioral state is used as an indicator of how to change the parameters. That is to say that the frequency, pulse width and voltage of stimulation are adjusted based on the positive response of the symptoms of each patient and simultaneous avoidance of side-effects (Dayal et al., 2017; Kringelbach, Jenkinson, Owen, & Aziz, 2007). It is evident that tDCS of both the normal and the diseased brain depends on a number of factors such as the stimulation parameters including the electrode localization, duration and intensity (see Table 5 and Figure 34) of stimulation and also the patient characteristics such as age, disease stage, years of education and premorbid level of functioning which influence cognitive reserve. The studies we reviewed above show remarkable differences regarding the criteria for selecting the patients, the placement of the electrodes, the duration and intensity of

stimulation (see Tables 4 and 5) and this makes it very difficult to compare the results across studies. More research into the complex dynamics of the current flow it is essential before obtaining a definitive optimization of stimulation protocols (see De Berker et al.(Berker, Bikson, & Bestmann, 2013)).

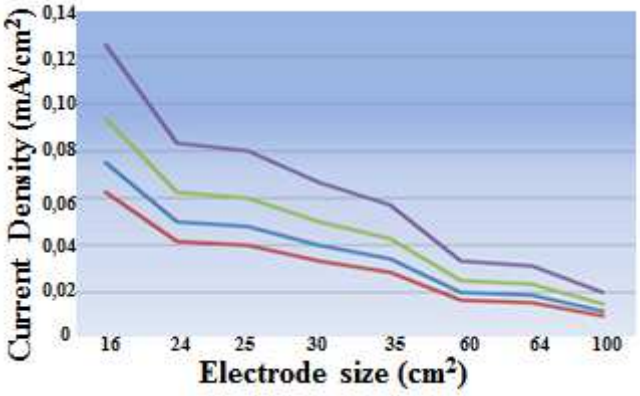


Figure 34: *Current Density (mA/cm²) as a function of electrode size.*

	Max Current Intensity (mA)			
Electrode size (cm²)	**1**	**1,2**	**1,5**	**2**
16	0,063	0,075	0,094	0,130
24	0,042	0,050	0,062	0,083
25	0,040	0,048	0,060	0,080
30	0,033	0,040	0,050	0,067
35	0,029	0,034	0,043	0,057
60	0,017	0,020	0,025	0,033
64	0,016	0,019	0,023	0,031
100	0,010	0,012	0,015	0,020

Table 5: *Current Density (mA/cm²) of different electrode dimensions.*

Further research in this area may include an integration of data coming from other techniques such as functional magnetic resonance imaging (fMRI) and magnetoenchephalografy (MEG). In the coming years, it is important to work towards optimizing tDCS protocols for cognitive rehabilitation based on the initial response of each patient to this therapeutic application.

State of the brain during stimulation

An important and fundamental question that remains to be addressed is "Why does depolarizing cells by administering a very weak current in the brain modify elaborate cognitive processes?" The theoretical model that may be relevant to answering this complex question is stochastic resonance (SR). SR has been observed throughout nature and it has been reported in physiological neural populations and networks (McDonnell & Ward, 2011). "*SR is observed when noise added to a system changes the system's behavior. Stochastic resonance (SR) is a phenomenon in which a signal that is normally too weak to be detected by a sensor, can be enhanced by adding white noise to the signal, which contains a spectrum of frequencies. A proportioned amount of added noise results in the maximum enhancement a disproportionate noise intensity degrade detectability or information"* (Moss, 2004).

Along similar lines, conceptualizing the administration of tDCS as adding noise to the brain system, one can argue that when a proportionate amount of noise enters the system it would maximize behavioral performance, and conversely if disproportionate noise enters the system it would not produce any effect or worse behavioral performance. This model seems appropriate to explain the high variability and the lack of statistical power reported in tDCS studies which is increasing the skepticism about the reliability and efficacy of such techniques (Bestmann & Walsh, 2017; Horvath et al., 2015; Jacobson et al., 2011; Medina & Cason, 2017). The implication of the SR model is that the activity status of the system is important. In this case the system is the brain. It follows that the activity of the brain during tDCS is extremely important in determining the overall effect of the stimulation as previously suggested by Silvanto and collaborators (Silvanto, Muggleton, & Walsh, 2008) and more recently by Miniussi and collaborators (Miniussi, Harris, & Ruzzoli, 2013). First, a critical factor which is necessary to consider is whether

stimulation should be applied during behavioral / cognitive treatment or whether stimulation should be applied offline. Second, following the SR model, it is necessary to consider how many sessions are needed to change the behavior of the 'brain system'. Third, not only the timing of stimulation and the number of sessions but also the difficulty of the task or training must be considered. Depending on the level of difficulty of the task that the patients have to engage in, more or less cognitive resources would be required, which is also an important variable. Fourth, in measuring cognitive performance it is needful to be aware of practice effect–related gains that could result in type 1 or type 2 errors in trials. Fifth, it is extremely important to determine whether any improvement generalized on untrained cognitive tasks. Fifth, Evidence indicates that cognitive enhancement can occur at the expense of other cognitive functions (Iuculano & Cohen Kadosh, 2013). To our knowledge very few publications in the literature have also measured other cognitive domains (different from that central for the study) to control for possible cognitive side effects. Future studies should consider all these factors for a more effective therapeutic protocol. The present review considered the application of tDCS for the cognitive rehabilitation of four neurocognitive disorders : Parkinson's Disease, Alzheimer's Disease, Unilateral Hemispatial Neglect and Aphasia. While in PD there is a general agreement on the parameters of stimulation, what might constitute the most sensitive test to measure t-DCS efficacy on cognitive domains remains unclear. By contrast, for AD, unilateral neglect and aphasia, the variability across studies in the stimulation parameters used, the target site of tDCS stimulation and on the intensity of the stimulation, makes drawing firm conclusions about efficacy more difficult. Nevertheless, most of the studies reviewed reported a positive effect of tDCS in all these neurocognitive disorders. However, in cognitive rehabilitation it is critical to move beyond statistical significance and consider clinical significance of effects. There is still no consensus on

which is an acceptable level of sustainability. Such positive evidence of tDCS-induced cognitive benefit cannot be considered as fully reliable due to methodological limits of the studies, particularly the lack of long-term follow-up to establish the durability and longevity of the observed beneficial effects and specific testing to establish whether the beneficial effects of tDCS observed in the laboratory/clinic generalized to everyday cognitive functioning and activities of daily living. Production of long-lasting and generalizable cognitive improvement by tDCS is essential to ensure clinical significance and meaningfulness of the benefits. We believe it is important to have guidelines that serve as a reference point. The field may benefit from drawing up some guidelines for application of tDCS as a therapeutic approach for NCDs.

5 APPLICATION OF ONLINE TRANSCRANIAL ALTERNATING CURRENT STIMULATION IN THE STUDY OF AUTOMATIC MOTOR INHIBITION

Summary

Automatic motor inhibition is an important and adaptive process through which an activated motor plan is suppressed if the movement is not intended to be executed. Neuronal networks are characterized by oscillatory activity. In the brain, a large variety of rhythms have been described that differ in their frequency, origin and reactivity to changes in task demands. Recent studies have demonstrated that active cortical networks are susceptible to weak sinusoidal perturbations of exogenous electric fields.

The aim of this study was to investigate the frequency-specific effect of transcranial alternate current stimulation (tACS) over the automatic control of movement in healthy volunteers. We hypothesized that applying two different tACS frequencies during a visuo-motor task would result in different behavioural effects Methods: In this study we used tACS to interact non-invasively with the ongoing task-related oscillatory activity. Stimulation was delivered at alpha (10 Hz) and beta (20 Hz) frequency over the supplementary motor area and the primary motor cortex (SMA-M1) connections, which are part of the BG-cortical motor loop, during the execution of the subliminal masked prime task. We measured the effects on task performance and on motor cortex corticospinal excitability by means of motor evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS).Results indicate a specific effect of 10 and 20-Hz tACS on functional inhibition in the SMA-M1 circuit: behaviorally there is an interference in task-related automatic inhibition whereas at a neurophysiological level there is a modulation in excitability of M1.The current study provides novel evidence that automatic mechanisms of motor behaviour can be modulated by imposing synchronized electrical oscillatory activity upon motor cortical regions. Our study have important implications for cognitive neuroscience studies suggesting that use tACS might offer the

possibility to demonstrate a causal link between endogenous brain oscillations, specific exogenous alternate current frequencies and specific cognitive processes.

5.1.1 Introduction

Automatic motor inhibition has been shown to be an important and adaptive process through which an activated motor plan is suppressed if the movement is not intended to be executed. In movement disorders such as Parkinson's disease, this inhibition is disturbed and might partially explain the slowness to select the appropriate response (D'Ostilio, Cremers, Delvaux, Sadzot, & Garraux, 2013; D'Ostilio, Deville, et al., 2013). Automatic motor inhibition can be studied in the visual subliminal masked prime task. An arrow indicates to move in a Left/Right choice reaction. It is preceded at different intervals by a similar (or opposite) arrow that is then perceptually masked by an intervening stimulus. When the interval between the mask and the target stimuli is short (ISI<80 ms), reaction times (RT) are faster when prime and arrow stimuli point in the same direction (compatible trials) than if they point in the opposite direction (incompatible trials). This is known as the positive compatibility effect (PCE). If the interval is longer (typically, 80 ms < ISI <250 ms), the effect reverses (Negative Compatibility Effect (NCE)) so that compatible trials have a longer RT than non-compatible trials. The NCE has been interpreted as resulting from an automatic and unconscious (i.e. triggered by subliminal stimuli) inhibition of a motor plan that was automatically and unconsciously activated by the prime arrow. It demonstrates that stimuli that are not consciously perceived can have a strong influence on motor performance (Eimer & Schlaghecken, 1998; Eimer & Schlaghecken, 2003). When the interval between the mask and the target is even longer (ISI>250) the PCE returns. Thus, alternating cycles of activation and inhibition occur in the competitive interactions between response alternatives (Praamstra & Seiss, 2005; Sumner & Brandwood, 2008).

Event-related fMRI (functional magnetic resonance imaging) shows BOLD (blood oxygenation level dependent) related activity in the SMA (supplementary motor area) and the striatum during the execution of the subliminal masked prime task consistent with the idea that these areas are part of a basal ganglia (BG)-cortical motor loop network responsible for the automatic motor inhibition of the prime (D'Ostilio et al., 2012; D'Ostilio, Deville, et al., 2013). Moreover a clinical lesion study shows that damage to the SMA (supplementary motor cortex) disrupts automatic inhibition measured by NCE (Sumner et al., 2007). Other forms of motor inhibition, such as volitional stopping of an ongoing movement also have been shown to involve similar circuitry. Electrophysiologically this has been linked with an increase in beta activity recorded in surface EEG or from deep brain electrodes (Kühn et al., 2004; N. C. Swann et al., 2012).The purpose of the present study was to test whether synchronized activity at this frequency is also relevant for automatic suppression of movement in the masked prime task. To do this we used transcranial alternating current (tACS) applied through scalp electrodes to modulate rhythmic activity in cortex and tested how this affected performance. Even if tACS is only a weak stimulus, there is mounting evidence that it can interact with ongoing oscillations in the brain. Work in animals has shown that relatively weak alternating electric fields applied through the skull can entrain spiking activity of neurons in widespread cortical areas shape cortical network dynamics (Fröhlich & McCormick, 2010b; Ozen et al., 2010). Data in humans are also consistent with the notion that tACS influences ongoing brain activity (Herrmann et al., 2013; Herrmann, Strüber, Helfrich, & Engel, 2016). It has been suggested that the application of tACS at a frequency matched to the frequency of endogenous oscillations can enhance those oscillations (Zaehle et al., 2010).

In the present experiments we applied tACS simultaneously to both the SMA and M1 since they are important nodes in the putative system for motor inhibition. We compared the effect of two different frequencies of tACS in the alpha and beta range. We expected that automatic inhibition would be affected by tACS in the alpha range since previous work has shown that EEG oscillations in this range are a neurophysiological marker of automatic motor control (Wach et al., 2013a). As a control we tested effects of tACS at beta frequency since oscillatory activity in this range might mediate the control of more complex movements. We measured the effects of tACS on performance of the masked prime task.

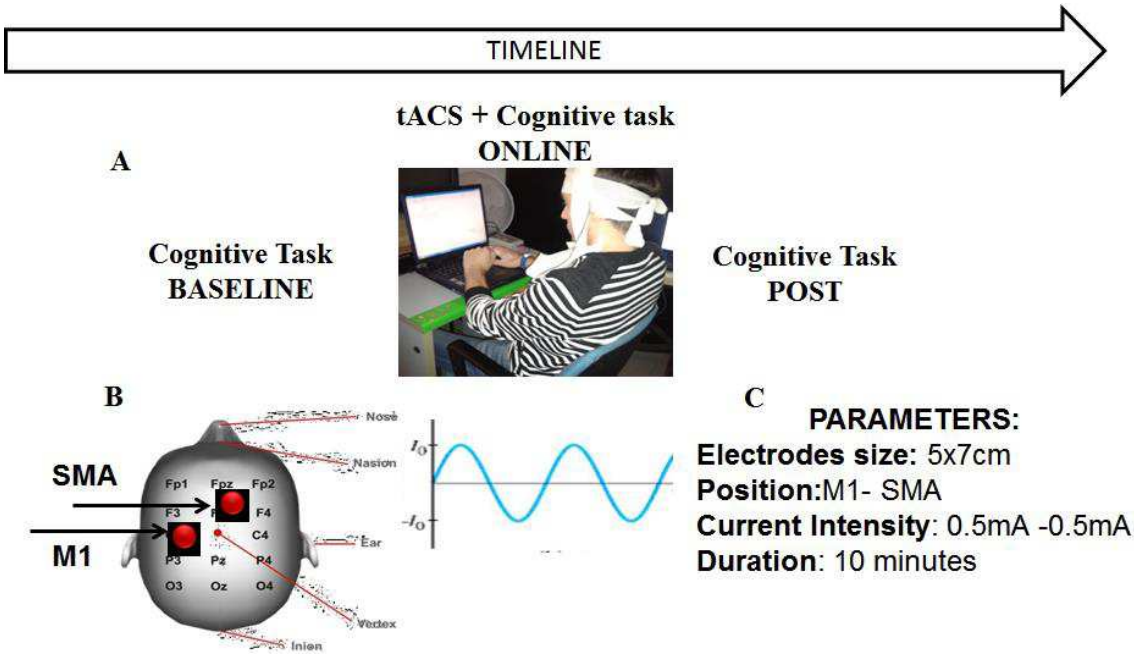


Figure 35: *A: Experimental procedure. B:Electrode montage on Primary motor (M1) cortex and supplementary motor area (SMA). C: tACS.*

5.1.2 Materials and Methods

Participants

Fifteen healthy volunteers (8 females, 26-33,mean age= 29 years) with no history of neurological, psychiatric, or other medical problems and no contraindications to TMS and tDCS (Rossi et al., 2009) participated in the experiment. They reported no history of neurological or psychiatric disease. They also stated that they did not take drugs or alcohol in the days preceding the experiments. Subjects were fully informed of the nature of the research and signed an informed consent before starting the experiment. The study was approved by the local ethical committee.

TMS of motor cortex to find the first dorsal interosseous hotspot:

TMS was performed using a Magstim 200 stimulator (Magstim, Whiteland, Dyfed, UK) connected to a figure-of-eight coil with an internal wing diameter of 7 cm. Motor cortex TMS readily evokes EMG responses in contralateral muscles referred to as a motor evoked potential (MEP) which can be recorded on electromyography (Day et al., 1987; J C Rothwell, 1997). The coil was held tangentially to the skull, with the handle pointing backward and laterally at 45° from midline, resulting in a posterior–anterior direction of current flow in the brain. FDI (i.e. hot spot) was determined before each experiment. In this determination, we stimulated several positions 0.5 cm distant from each other using the same intensity. The hot spot was defined as the site at which the largest responses were elicited.

tACS stimulation: tACS was delivered by a battery driven current stimulator (BrainStim, EMS, Bologna, Italy) through surface saline-soaked sponge electrodes (size, 5 × 7 cm). Stimulation waveform was sinusoidal applied at 10 Hz and 20 Hz at an intensity of 1 mA (-0.5/+0.5) fade in/out 30 sec. for a duration of 10 min (i.e. the duration of the cognitive task). For sham stimulation tACS was terminated after 30 seconds in order to elicit the typical tingling sensation under the electrode at the beginning of stimulation. Stimulation

was delivered via sponge electrodes one attached to the scalp over the left M1(FDI hotspot), while the other was placed over the SMA (i.e. (three cm anterior to CZ as suggest from previous study (Matsunaga et al., 2005). The setup was optimized to ensure that impedance, as measured by the stimulation device, was <10 kΩ. tACS was administered in a within-subject design with two active conditions and one sham condition. A questionnaire to measure the feelings elicited by stimulation was given at the end of each experimental session (Fertonani, Ferrari, & Miniussi, 2015) and participants reported that they only perceived phosphenes the first few seconds of tACS stimulation in all three stimulation sessions (10Hz, 20Hz, sham).

Task procedure:

In brief, each trial of the masked prime task started with a fixation cross displayed at the center of the screen. After a blank screen of 300 ms, a prime stimulus, consisting in double leftward (<<) or rightward (>>) pointing arrows, was centrally presented for 17 ms at fixation. Refresh rate of the monitor 60 Hz. The prime was immediately followed by a mask stimulus displayed for 100 ms that consisted in 30 randomly oriented lines covering a rectangular area centered on the prime display area. Following this backward mask stimulus, a target stimulus, whose physical properties were identical to that of the prime stimulus, was presented for 100 ms in the centre of the screen. The direction of the target stimulus was either identical (compatible condition) or opposite (incompatible condition) to the prime stimulus (Figure 36). Participants were asked to respond to the target stimuli as quickly and as accurately as possible by pressing a button with right hand. Visual stimuli were generated and subject responses recorded by a personal computer using COGENT Cognitive interface software (COGENT 2000, Department of Imaging Neuroscience, London, UK) implemented in Matlab (Mathworks, Sherborn,

MA). Here, there were five main experimental conditions defined by the time elapsed between the mask display onset and the target display onset: 0, 100, 150, 200 and 250 ms. Longer Inter Stimulus Intervals (ISI) were obtained by modulating the time duration of a blank screen presented between the mask display offset and the target display onset.

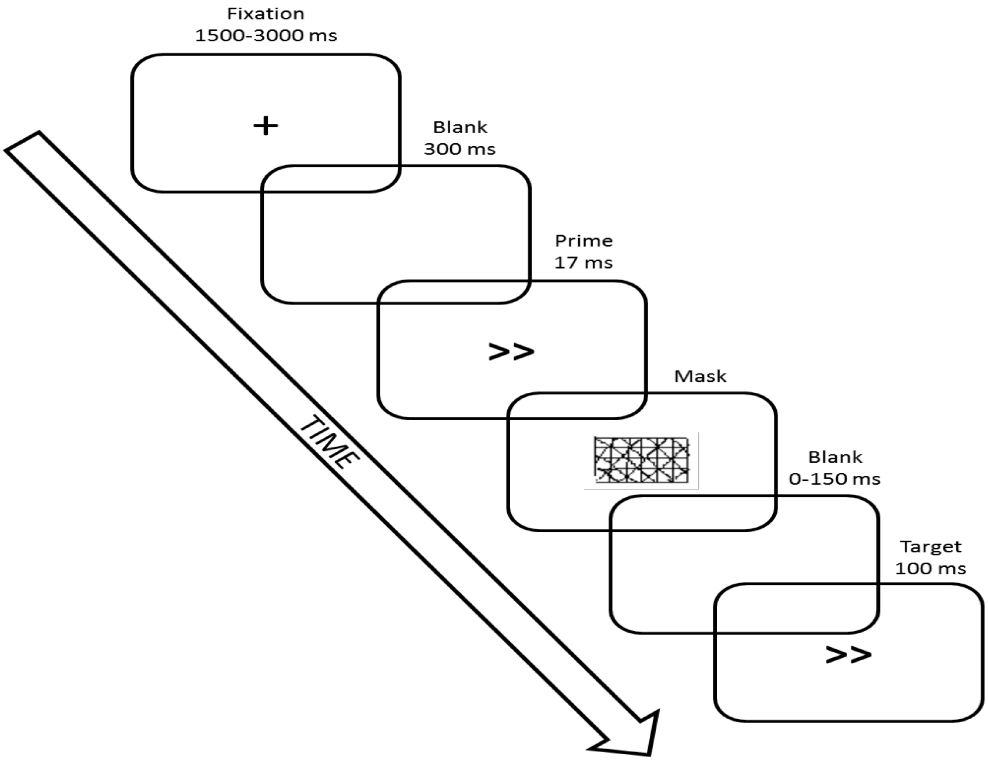


Figure 35: *Schematic illustration of the task for a compatible trial the duration of the blank screen before the arrow target (0–50–100–150 ms) determined the ISI (100–150–200–250).*

Experimental Procedures

Participants were seated comfortably in a chair with the right arm resting on a pillow throughout the experiment. Firstly, surface EMG electrodes were applied on the right hand FDI muscle; the motor cortical representation (hotspot) was then identified and the intensity to evoked 1mV motor threshold. Subsequently 25 MEPs were recorded before task execution for baseline (T0). The subjects were then asked to perform the visual

prime motor task that last 10 min and immediately afterwards 25 MEPs were recorded for baseline before tACS (T1). Whereupon tACS electrodes were applied on the scalp one on the SMA (three cm forward the CZ) and one over the contralateral left M1 over the FDI hotspot. The mild itching or tingling sensation under the electrodes was reported only during the ramping up phase of stimulation. The task was performed before, during and after stimulation. In addition, MEPs were recorded at baseline before (T0-T1), after tACS (T2) and a third time after the last session of the subliminal task (T3). Each participant participated in three sessions, the three stimulation sessions (sham,10hz, 20hz) were tested in a pseudorandomized order across the days (Figure 35). The study was approved by the local ethical committee and was conducted in line with the Declaration of Helsinki.

Data analysis

Behavioural : Mean reaction times (RT) were calculated for each ISI condition (Table 6). Trials with incorrect responses and RT longer than 1 second were discarded from the RT analysis. A repeated measures 3-way ANOVA with main effects of stimulation (sham,10Hz,20Hz), prime-target ISI (0,100,150,200,250) and compatibility (compatible, incompatible) was used to compare the RT in compatible and incompatible trials at each ISI in the three baseline sessions. To evaluate effects of tACS on RTs, a second 3-way repeated measures ANOVA with main factors of 'time of task execution' (baseline, online, post), ISI(0,100,150,200,250) and compatibility (compatible ,incompatible) were used to compare RT separately in the 10Hz condition , in the 20 Hz condition, in the sham condition. To measure a possible interaction of tACS and compatibility we performed a repeated measures ANOVA on the online RT condition at each ISI with two within-subject factors: compatibility (compatible, incompatible) and stimulation (sham,10Hz,20Hz). The compatibility effect (CE) was obtained by subtracting the RT of

incompatible and compatible trials at each ISI (Table 7). To measure the effects of the tACS stimulation, we calculated the difference between: Δ1=(CE ONLINE) – (CE BASELINE) and Δ2=(CE POST) – (CE BASELINE). A repeated measures ANOVA on CEΔ1 with factors of stimulation(sham,10Hz,20Hz) and ISI (100,150,200,250) was used to compare the effects of the tACS protocol online during the execution of the cognitive task.

A repeated measures ANOVA on CEΔ2 for the factors stimulation (sham,10Hz,20Hz) and ISI (100,150,200,250) was used to compare the after effects of the tACS protocol on the execution of the subliminal task.

5.1.3 Results

Reaction Times

We replicated the masked prime effects described by others. For the baseline sessions (pre tACS) a repeated measures ANOVA on RT revealed a significant ISI*compatibility interaction ($F(4,56) = 41.71$; $p = < 0.001$) which was due to a faster RT in compatible than incompatible trials at 0-ISI (PCE: diff = 38.72ms) and the reverse (NCE) at 100-ISI (NCE: diff= -8.76ms), at 150- ISI (NCE: diff= -19.48ms) and at 200-ISI (NCE diff=-5.64ms). A PCE returned at 250-ISI (PCE: diff=2.38ms).The main effect of session (i.e. control, 10 Hz, 20 Hz) was not significant, $F(2,28) = .048$, $p > .05$ indicating that there were no differences between sessions at baseline.

			ISI-0			ISI-100			ISI-150			ISI-200			ISI-250		
			Comp	Incomp	CE	Comp	Incomp	CE	Comp	Incomp	CE	Comp	Incomp	CE	Comp	Incomp	CE
Baseline	10Hz	mean	416,98	453,05	36,07	427,19	421,72	-5,47	394,30	379,37	-14,93	370,46	363,25	-7,21	360,77	355,37	-5,41
		SD	28,07	32,92		39,67	41,56		35,99	33,87		36,97	37,84		43,19	39,92	
	20Hz	mean	417,37	456,01	38,64	419,97	408,70	-11,27	393,30	376,54	-16,76	367,54	362,07	-5,47	350,67	357,95	7,28
		SD	28,56	35,41		29,09	34,18		33,89	30,76		28,74	33,04		23,43	35,20	
	Sham	mean	395,70	435,92	40,22	435,81	424,71	-11,10	412,42	386,52	-25,90	378,42	373,38	-5,04	366,17	370,31	4,14
		SD	28,45	31,81		25,34	33,98		31,04	28,76		30,96	36,95		32,98	36,35	
			ISI-0			ISI-100			ISI-150			ISI-200			ISI-250		
			Comp	Incomp		Comp	Incomp		Comp	Incomp		Comp	Incomp		Comp	Incomp	
Online	10Hz	mean	351,50	372,27	20,77	420,42	407,26	-13,16	387,93	378,46	-9,47	363,43	366,62	3,19	346,83	359,54	12,71
		SD	56,46	60,97		31,23	29,22		33,99	35,98		30,91	28,47		32,25	31,83	
	20Hz	mean	356,74	389,59	32,86	419,86	405,34	-14,52	388,51	373,43	-15,07	365,37	358,69	-6,67	350,80	349,16	-1,64
		SD	25,66	27,47		23,22	27,67		28,95	31,66		26,84	25,84		27,66	33,16	
	Sham	mean	349,80	378,09	28,29	413,09	399,05	-14,04	376,97	365,99	-10,97	356,21	344,57	-11,64	338,34	345,44	7,11
		SD	22,20	25,13		25,57	29,38		26,21	20,46		20,46	26,43		22,98	37,28	
			ISI-0			ISI-100			ISI-150			ISI-200			ISI-250		
			Comp	Incomp		Comp	Incomp		Comp	Incomp		Comp	Incomp		Comp	Incomp	
Post	10Hz	mean	406,46	426,99	20,53	418,64	405,04	-13,60	378,70	369,30	-9,39	357,79	352,22	-5,57	346,32	343,24	-3,07
		SD	47,94	34,64		21,30	29,97		23,96	28,77		25,84	37,65		26,65	42,60	
	20Hz	mean	344,43	373,60	29,17	412,39	405,27	-7,12	381,09	366,30	-14,79	361,34	352,73	-8,61	336,92	345,32	8,39
		SD	23,37	27,73		26,66	29,78		31,70	28,19		34,49	32,32		28,57	39,40	
	sham	mean	363,52	397,53	34,01	404,10	399,80	-4,30	373,45	366,30	-7,15	351,10	345,54	-5,56	334,89	339,37	4,48
		SD	18,14	27,35		20,78	29,09		23,11	26,11		21,62	33,61		23,00	34,76	

Table 6: *Mean Reaction Time in milliseconds and standard deviation for all tACS stimulation conditions(10Hz, 20Hz,sham) at each time point (Baseline, Online, Post) for all compatible and incompatible conditions at each Prime-Target ISI. (ISI=inter stimulus interval, Comp=compatible, Incomp= incompatible, CE=Compatibility Effect, SD=Standard Deviation).*

	ISI-0		ISI-100		ISI-150		ISI-200		ISI-250	
	Δ1CE	Δ2CE	Δ1CE	Δ2CE	Δ1CE	Δ2CE	Δ1CE	Δ2CE	Δ1CE	Δ2CE
10Hzmean	-15,30	-15,54	-7,69	-8,13	5,47	5,54	10,40	1,64	18,11	-21,18
20Hzmean	-5,79	-9,48	-3,25	4,15	1,68	1,97	-1,21	-3,14	-8,92	17,31
sham mean	-11,93	-6,21	-2,93	6,81	14,92	18,74	-6,60	-0,52	2,97	1,52

Table 7: *Mean Δ1 and Δ2 CE at each ISI.CEΔ1 is the difference in the compatibility effect during stimulation versus baseline; CEΔ2 is the difference between stimulation and post-stimulation sessions.(ISI=inter stimulus interval, CE=Compatibility Effects).*

Global Reaction Time

We then analysed whether tACS changed the time course of masked prime effects with 3 way ANOVAs on each tACS condition separately. For both sham and 10 Hz tACS there was no significant main effect of 'time of task execution', indicating that these conditions had no effect on RTs . However, there was a significant main effect of 'time of task execution', F(1.06, 13.77) = 6.88; p=0.02) for 20Hz tACS. Post-Hoc analysis revealed there was a significant difference between baseline (M= 393.02,SE=9.50) versus online (M=376.49,SE=7.91) between baseline (M= 393.02,SE=9.50) versus post (M=369.90,SE=7.16) and between online (M=376.49,SE=7.91) versus post (M=369.90,SE=7.16) indicating a significant reduction of RT during and after 20Hz tACS. To analyze these effects in more detail we conducted a 2-way repetitive measure ANOVA within-subject factors of compatibility (compatible, incompatible) and stimulation (sham, 10Hz, 20Hz) at each ISI during the stimulation session. This revealed a significant stimulation*compatibility interaction at ISI 200 (F(2,26)= 3.199, p=0.05) which is analyzed in more detail below

Compatibility Effects

CEΔ1 is the difference in the compatibility effect during stimulation versus baseline; CEΔ2 is the difference between stimulation and post-stimulation sessions (see Figure 37). During the period of the NCE (i.e. ISI 200, 250 ms), a positive value for CEΔ1 indicates that the NCE during stimulation (i.e. the paradoxical increase in reaction time when the prime is compatible compared with an incompatible prime) is less than that at baseline. A repeated measures ANOVA on CEΔ1 showed a significant main effect of stimulation ($F(2,26)=3.787$, $p=0.036$) as well as a stimulation*ISI interaction ($F(6,78)=2.742$,$p=0.018$). Post-Hoc analysis revealed that at ISI 250 there was significant difference between 10Hz ($M=19.27$,$SE=5.23$) versus sham ($M=2.53$, $SE=5.57$) ($t(14)=18.40$, $p=0.025$), and between the effects of 20Hz ($M=-8.27$, $SE=5.09$) compared to 10Hz ($M=19.27$, $SE=5.23$)($t(14)= - 27.54$, $p<0.001$), indicating that the two frequencies of stimulation have distinct effects on the compatibility effect. 10 Hz tACS appears to reduce the NCE compared to sham and 20 Hz tACS; 20 Hz tACS increased the NCE. At ISI 200 there was a significant difference of 10Hz ($M=10.56$,$SE=5.71$) versus sham ($M=-5.62$,$SE=5.62$) ($t(14)= -16.19$, $p=0.03$), indicating that 10Hz reduced the NCE (Figure 37). The repeated measures ANOVA on CEΔ2 showed that the main effect of stimulation was not significant ($F(2,26)=.426$, $p>0.05$) indicating that the effects of stimulation may have worn off.

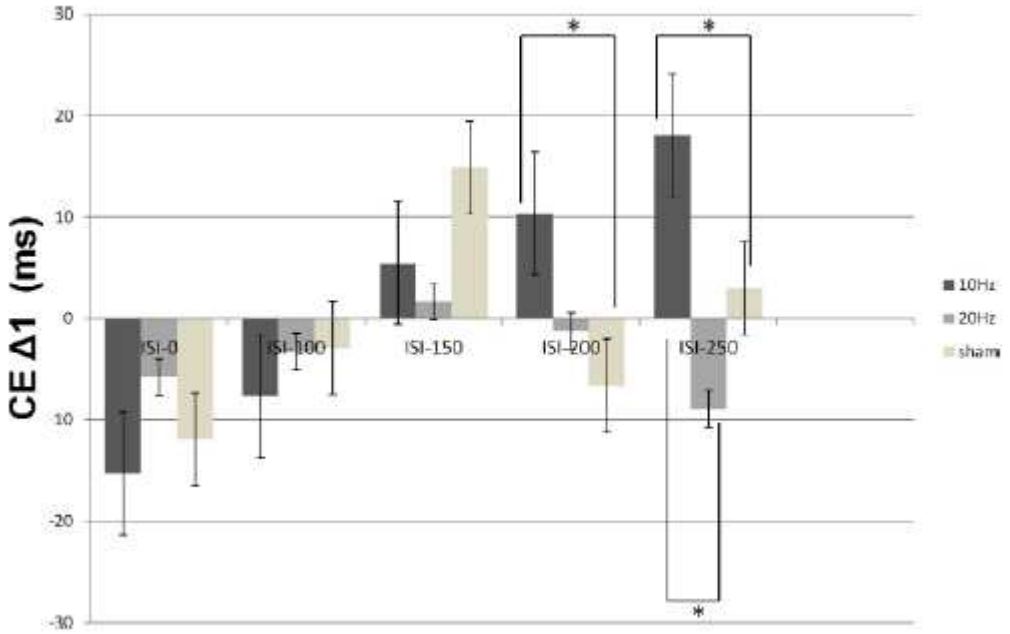


Figure 37: *Modulation of compatibility effects in ms during the tACS stimulation conditions (10Hz, 20Hz,sham) for each Prime-Target inter stimuli intervals (ISIs). Verticals line represent standard errors. (CE= Compatibility Effect).*

5.1.4 Discussion

tACS was applied during a visuo-motor subliminal masked prime task in order to investigate the effect of 10 Hz and 20 Hz stimulation on automatic motor inhibition during the negative compatibility effect. We found that 10 Hz tACS, compared to sham, reduced the negative compatibility effect (slower responding to a compatible prime) at ISI = 200 and 250ms. In contrast 20 Hz tACS increased the NCE effect at ISI = 250ms.

Electroencephalographic (EEG) and local field potential (LFP) studies have seen rising interest in oscillations occurring in beta band (13Hz-30Hz) particularly in the human motor system (Gaynor et al., 2008; Kühn et al., 2004, 2006). There is evidence that beta oscillations are pronounced during maintenance of tonic motor output and reduce during periods of movement (Stuart N Baker, 2007). Recent evidence have also noted an increase of beta frequency during response inhibition, such as successful inhibition in Go/No Go tasks (N. C. Swann et al., 2012; N. Swann et al., 2009a). The current concept is that response inhibition is implemented synchronization of beta activity within a

network consisting of basal ganglia and motor cortical areas including SMA and M1. The NCE has been interpreted as a process of inhibitory control and therefore the small increase in NCE during 20 Hz tACS at ISI 250ms is consistent with the idea that tACS enhances beta activity in the motor network thereby improving NCE. A similar argument was made to account for the slowing of movement execution during application of beta tACS over M1 by Pogosyan et al (Pogosyan et al., 2009). However, we should note that our stimulation was not time locked to ongoing beta activity in the EEG, so that the overall beta facilitation may have been small. A larger effect might have been observed if we had been able to phase lock tACS to the ongoing natural frequency of beta activity in each individual (see Brittain et al) (Brittain et al., 2013). Application of 10 Hz tACS had the opposite effect and reduced the duration of the NCE, effectively making the process of automatic inhibition less powerful. It could be that 10 Hz tACS interfered with activity in the beta range, favouring movement rather than stopping. However, this could only be confirmed by simultaneous recording of ongoing EEG activity in a future study.

Interestingly, 10 and 20 Hz tACS also had different effects on excitability of M1, as tested with TMS. 20 Hz tACS reduced MEP amplitudes, whereas there was no change after 10 Hz tACS (see chapter 6). The reduction in excitability after 20 Hz tACS is consistent with strengthening of the NCE. However, given that the MEPs were evaluated after tACS whereas the main effect on the NCE occurred during tACS, it is possible that different mechanisms were involved. Indeed, there is not much evidence that brain rhythms entrained by tACS continue to be enhanced for more than a few seconds after offset of tACS (Vossen et al., 2014a). An important caveat to the present study is that given our electrode locations, we effectively applied tACS out of phase to M1 and SMA. We did not have two different tACS machines to allow us to apply in-phase stimulation to

both areas, and therefore do not know whether the effects would differ. Nevertheless this would be a fruitful field for further research.

Conclusions

The current study provides novel evidence that automatic mechanisms of motor behaviour can be modulated by imposing synchronized electrical oscillatory activity upon motor cortical regions. We argue that the effects exerted by tACS during task appear to depend on aspecific neuronal activation which is related to the nature of the task. Indeed, the task adopted in this study elicits the activation of automatic inhibitory processes which are related to an upregulation of beta oscillations. Our study has implications for cognitive neuroscience studies suggesting that use tACS might offer the possibility to demonstrate a causal link between endogenous brain oscillations and specific cognitive processes. The present study is also relevant to potential clinical applications of tACS. Our study support the emerging view that giving stimulation during a particular cognitive state could be more effective in modulating brain activity. Future studies are also important to elucidate the possibility that alternating current rather than constant current might be more effective in shaping network dynamics in clinical applications.

6 DIVERSE EFFECTS OF 10 Hz AND 20 Hz STIMULATION ON CORTICOSPINAL EXCITABILITY: A COMBINED A COMBINED tACS-TMS STUDY

6.1.1 Introduction

Classically is has been demonstrated that it is possible to measure the effect of the application of weak transcranial current stimulation (tCS) adopting transcranial magnetic stimulation (TMS). These model propose that the elecromyographical activity evoked non invasively by a single pulse TMS reflects the excitability of the motor system. Specifically the amplitude of the TMS readily evokes elecromyographical responses in contralateral muscles referred to as a motor evoked potential (MEP) which can be recorded on electromyography (EMG). Several evidence demonstrate that tDCS scalp surface anodal and cathodal electrodes injecting low amplitude direct currents (0.5-2mA) through the head for few seconds to several minutes is able to alter the cortical excitability. Generally if the anode is placed above the motor cortex, after DC stimulation , single pulse TMS will result in a larger MEP. If the cathode is placed over the motor cortex, the MEP size will be reduced (Nitsche & Paulus, 2000). Thus, long-lasting and polarity-dependent changes in neural excitability of the human cortex are elicited. This effect is conceivably due to depolarization of somatic membrane potentials by anodal currents and hyperpolarization of soma by cathodal currents, as observed in animal studies (Bindmann, Lippold, & Redfearn, 1964) Several studies have been performed in humans in order to understand the physiological mechanisms of tDCS. It has been shown that the effects on the MEP can be modified, prolonged or even reversed by drugs acting on the central nervous system (Stagg & Nitsche, 2011). Importantly, it seems that neuroplastic after-effects of tDCS are NMDA-receptor dependent (Liebetanz et al., 2002). Recent advance of transcranial current stimulation (tCS) have proposed tACS as a newly developed method. In contrast to tDCS that uses direct current (DC), tACS allows delivery of alternating current at different frequencies. tACS has been used to manipulate ongoing brain oscillations in a controllable way. In this study we measured the effects of

tACS applied on primary motor cortex (M1) and supplementary motor area (SMA) on motor corticospinal excitability by means of motor evoked potentials (MEPs) evoked by single pulse transcranial magnetic stimulation (sTMS) over primary motor cortex (M1).

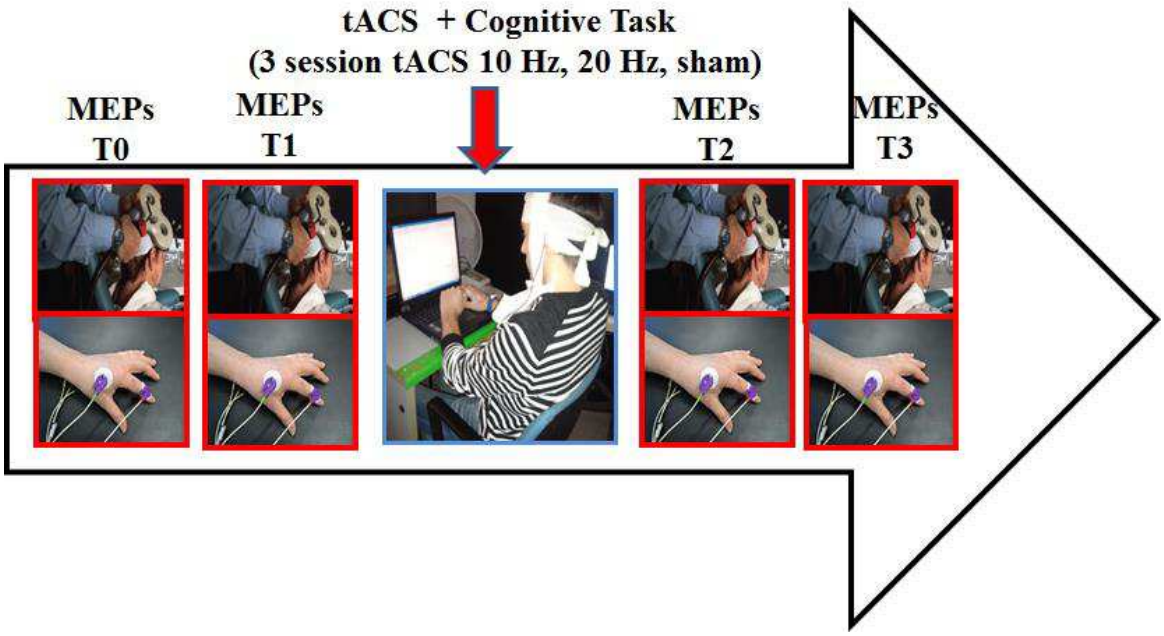


Figure 38: *A: Experimental procedure. MEPs= motor evoked potentials, tACS= transcranial alternating stimulation.*

6.1.2 Materials and Methods

Participants

Fifteen healthy volunteers (8 females, 26-33,mean age= 29 years) with no history of neurological, psychiatric, or other medical problems and no contraindications to TMS and tDCS (Rossi et al., 2009) participated in the experiment. They reported no history of neurological or psychiatric disease. They also stated that they did not take drugs or alcohol in the days preceding the experiments. Subjects were fully informed of the nature of the research and signed an informed consent before starting the experiment. The study

was approved by the local ethical committee and was conducted in line with the Declaration of Helsinki.

Electromyography recordings (EMG): Surface EMG was recorded from the right First Dorsal Interosseous muscle (FDI) muscle via Ag/AgCl electrodes in a belly-tendon montage (Myohandy Matrix Line — Micromed Srl, Mogliano Veneto, Italy); raw signals were sampled at 2.5 kHz and band-pass filtered at 50–1000 Hz. MEP amplitudes were measured peak-to-peak.

TMS of motor cortex to elicit motor evoked potential (MEP):

TMS was performed using a Magstim 200 stimulator (Magstim, Whiteland, Dyfed, UK) connected to a figure-of-eight coil with an internal wing diameter of 7 cm. Motor cortex TMS readily evokes EMG responses in contralateral muscles referred to as a motor evoked potential (MEP) which can be recorded on electromyography (Day et al., 1987; Rothwell, 1997). The coil was held tangentially to the skull, with the handle pointing backward and laterally at 45° from midline, resulting in a posterior–anterior direction of current flow in the brain. FDI (i.e. hot spot) was determined before each experiment. In this determination, we stimulated several positions 0.5 cm distant from each other using the same intensity. The hot spot was defined as the site at which the largest responses were elicited. This position was marked using a red pencil on the scalp for repositioning the coil. Single-pulse TMS were delivered with an inter-stimulus interval (ISI) of 4.5–5.5s over the FDI hotspot at an intensity that evokes MEPs of about 1 mV over the left motor cortical representation of the right FDI in order to measure cortical excitability. We measured 25 MEPs at different time points : at baseline, directly after tACS and after the last session of the subliminal task.

tACS stimulation: tACS was delivered by a battery driven current stimulator (BrainStim, EMS, Bologna, Italy) through surface saline-soaked sponge electrodes (size, 5 × 7 cm). Stimulation waveform was sinusoidal applied at 10 Hz and 20 Hz at an

intensity of 1 mA (-0.5/+0.5) fade in/out 30 sec. for a duration of 10 min (i.e. the duration of the cognitive task). For sham stimulation tACS was terminated after 30 seconds in order to elicit the typical tingling sensation under the electrode at the beginning of stimulation. Stimulation was delivered via sponge electrodes one attached to the scalp over the left M1(FDI hotspot), while the other was placed over the SMA (i.e. (three cm anterior to CZ as suggest from previous study (Matsunaga et al., 2005). The setup was optimized to ensure that impedance, as measured by the stimulation device, was <10 kΩ. tACS was administered in a within-subject design with two active conditions and one sham condition. A questionnaire to measure the feelings elicited by stimulation was given at the end of each experimental session (Fertonani et al., 2015) and participants reported that they only perceived phosphenes the first few seconds of tACS stimulation in all three stimulation sessions (10Hz, 20Hz, sham).

Task procedure:

details of the task are reported in the chapter 5.

Experimental Procedures: Participants were seated comfortably in a chair with the right arm resting on a pillow throughout the experiment. Firstly, surface EMG electrodes were applied on the right hand FDI muscle; the motor cortical representation (hotspot) was then identified and the intensity to evoked 1mV motor threshold**.** Subsequently 25 MEPs were recorded before task execution for baseline (T0). The subjects were then asked to perform the visual prime motor task that last 10 min and immediately afterwards 25 MEPs were recorded for baseline before tACS (T1). Whereupon tACS electrodes were

applied on the scalp one on the SMA (three cm forward the CZ) and one over the contralateral left M1 over the FDI hotspot. The mild itching or tingling sensation under the electrodes was reported only during the ramping up phase of stimulation. The task was performed before, during and after stimulation. In addition, MEPs were recorded at baseline before (T0-T1), after tACS (T2) and a third time after the last session of the subliminal task (T3). Each participant participated in three sessions, the three stimulation sessions (sham,10hz, 20hz) were tested in a pseudorandomized order across the days (Figure 38).

Data analysis

MEPs:

We calculate the normalized MEPs amplitude ratio. A repeated measured ANOVA was performed on normalized MEPs amplitude ratio for the factors Stimulation (sham,10Hz,20Hz) and time (T2,T3). In all cases, Greenhouse-Geiser corrections were made when necessary for non-sphericity of the data

6.1.3 Results

Behavioural data analysis are reported in the chapter 6

MEP analysis:

Overall, 20 Hz stimulation reduced the MEP amplitude at T3. The repeated measures ANOVA revealed a significant main effect of stimulation ($F(2,26)=5.372$ $p=0.011$) and a stimulation*time interaction ($F(2,26)=7.56$) indicating significant difference in the effect of simulation condition over time. Post-Hoc analysis revealed T2 significant differences between 20Hz (M=0.92,SE=0.79) and 10Hz (M=1.11,SE=0.65) ($t(13)=-2.042$, $p=0.03$), and at T3 a statistically significant difference between 20Hz (M=0.68,SE=0.63) and 10Hz (M=1.12,SE=0.88) ($t(13)=-4.187$, $p=0.01$) and between 20Hz (M=0.68,SE=0.63) and sham (M=1.11,SE=095) ($t(14)=-4.824$, $p<0.001$) with no significant difference between

10Hz and Sham. Furthermore there is a significant difference between 20Hz T1 (M=0.92,SE=0.79) and 20Hz T2 (M=0.64,SE=0.68) (t(14)=3.305, p=0.005) suggesting that 20Hz produced a gradually increasing effect on MEP amplitude (Figure 39).

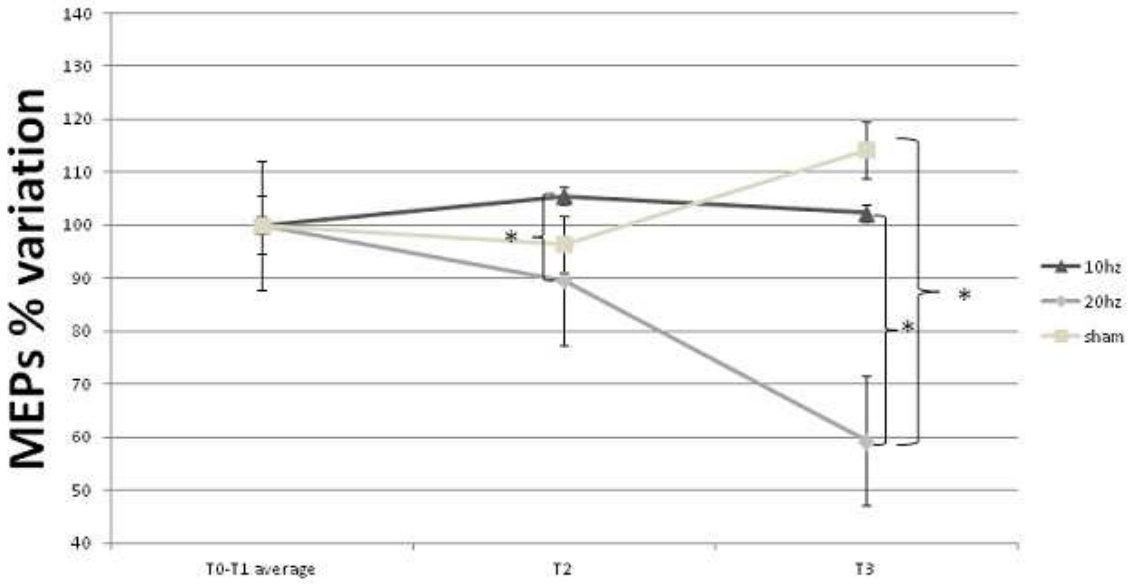


Figure 39: *Changes in amplitude of motor evoked potentials (MEPs) recorded on the First Dorsal Interosseous (FDI) muscle evoked by single pulse TMS for the three experimental conditions at each time point (Baseline, T2 and T3).*

6.1.4 Discussion

tACS was applied during subliminal masked prime task in order to investigate the effect of 10 Hz and 20 Hz after on motor cortical excitability. We found that 10 and 20 Hz tACS have different effects on excitability of M1, as tested by single pulse TMS. Previous reports highlight that the activity of the brain during tDCS is extremely important in determining the overall effect of the stimulation as previously suggested by Silvanto et al. (2008) and more recently by Miniussi et al. (2013). Related to this, Feurra and colleagues showed that the transcranial application of alternating current is able to modulate corticospinal excitability online, with frequency dependence. The authors

demonstrated a significant increase of motor evoked potentials (MEPs) during the local application of transcranial alternating current stimulation (tACS) at 20 Hz, while different tACS frequencies (5, 10, and 40 Hz) applied on the motor cortex were not effective. This results indicate frequency specific effects of tACS. Contrary, we found that 20Hz tACS reduce MEPs amplitude, we believe this is due to the nature of the behavioral task used which is able to activate inhibitory mechanisms that we hypothesized to reflect an upregulation in beta activity. In a subsequent study the author using an imagery task were able to demonstrate that the brain activity is able to modulate the effects of tACS on cortical excitability (Feurra et al., 2013). Here, tACS was applied during a masked prime task which it has been previously shown to elicit automatic motor inhibition. The current concept is that response inhibition is implemented synchronization of beta activity within a network consisting of basal ganglia and motor cortical areas including SMA and M1(primary motor cortex).

We found that 10 and 20 Hz tACS have different effects on excitability of M1, as assessed by single pulse TMS. Specifically 20 Hz tACS reduced MEP amplitudes, whereas there was no change after 10 Hz tACS. The reduction in excitability after 20 Hz tACS is consistent with strengthening of automatic motor inhibition (see chapter 5). However, given that the MEPs were evaluated after tACS whereas the main effect on the NCE occurred during tACS, it is possible that different mechanisms were involved.

There have been a number of previous reports of the effects of 10 and 20 Hz tACS on the excitability of M1. However they are difficult to compare directly with the present work because the position of the electrodes (usually C3 and supraorbital) are different than that used here (SMA and M1). Nevertheless, 10 Hz tACS was reported to produce only a trend toward MEP inhibition after 5 minutes of 10 Hz tACS stimulation (Antal et al.,

2008) whereas 20Hz tACS produced an increase of corticospinal excitability in one study (Feurra, Bianco, et al., 2011) but not another (Feurra et al., 2013).

An important caveat to the present study is that given our electrode locations, we effectively applied tACS out of phase to M1 and SMA. We did not have two different tACS machines to allow us to apply in-phase stimulation to both areas, and therefore do not know whether the effects would differ. Nevertheless this would be a fruitful field for further research.

Conclusions

The current study provides novel evidence on the influence of tACS on brain cortical excitability dynamics which appear to depend on the nature of the neuronal activation during the task. The present study is also relevant to potential clinical applications of tACS. Our study support the emerging view that giving stimulation during a particular cognitive state could be more effective in modulating brain activity. Future studies are also important to elucidate the possibility that alternating current rather than constant current might be more effective in shaping network dynamics in clinical applications.

7 EFFECTS OF 10 Hz AND 20 Hz STIMULATION ON ALPHA/BETA NEURONAL OSCILLATIONS: A COMBINED tACS-EEG STUDY

Summary

Oscillatory rhythms in the brain contribute to brain activity in a broad sense, ranging from sensory and motor functioning to high-level cognitive processes. Rhythmic transcranial alternating stimulation (tACS) may impact brain oscillations. These effects are thought to be related to interactions between ongoing brain oscillatory activity and the tACS-imposed oscillatory activity. Combined tACS-EEG approaches have been used to precisely characterize the neurophysiological basis of the abovementioned tACS-induced effects. The effects of tACS stimulation on electroencephalography (EEG) rhythms have been investigated. Adopting a 10 Hz tACS protocol, previous reports demonstrated a specific increment in EEG power spectral density (PSD) in the adjacent (8, 13) Hz band (i.e., α-band) during and after stimulation. Apart from the α-band there is scarce evidence of direct tACS-induced modulation of other brain rhythms. Nonetheless, by adopting a 20 Hz tACS frequency protocol over motor cortex, previous studies induced movement slowing and reported modulation of automatic motor inhibition. This evidence suggest that 20 Hz tACS stimulation interacts with the oscillatory activity in motor networks, namely the ß-band (13, 30) Hz. However, to date there is no direct EEG evidence for the modulation of sensorimotor β activity after 20 Hz tACS interventions. Here we employed a combined EEG-tACS approach in order to measure time-varying changes in α and β-bands following tACS stimulation. Stimulation was delivered at 10 Hz and 20 Hz frequency over the supplementary motor area and the primary motor cortex (simultaneous tACS of SMA-M1). We found that tACS caused both local and distant cortical dynamics changes. In particular, 20Hz tACS increased β-band PSD specifically over the sensorimotor cortex. Conversely, 10 Hz tACS increased α-band PSD over the occipital

cortex. These results provide evidence for the frequency and regional specific interaction between tACS frequency and EEG rhythms.

7.1.1 Introduction

Electroencephalography (EEG) reflects the oscillatory activity of large groups of neurons firing in concert. Oscillatory rhythms in the brain contribute to brain activity in a broad sense, ranging from sensory and motor functioning to high-level cognitive processes (Buzsáki, 2006; Lopes da Silva, 1991). Cyclic variations of neuronal excitability play a fundamental role in local and long distance communication between brain areas (Buzsaki & Draguhn, 2004). It has been proposed that rhythmic transcranial alternating stimulation (tACS) may impact brain oscillations, thus potentially modulating specific sensory, motor or higher cognitive processes. Supporting this view, the physiological basis of tACS has been investigated in animal models (for review see Reato et al., 2013), showing that this kind of stimulation induces subthreshold changes in the membrane potentials, altering the tendency of neurons to fire in response to a stimulus (Fröhlich & McCormick, 2010b; Ozen et al., 2010). In humans, promising results showed that tACS selectively modulate auditory, visual and tactile perception (Feurra et al., 2013; Kanai et al., 2008; Neuling, Rach, Wagner, Wolters, & Herrmann, 2012; Strüber, Rach, Trautmann-Lengsfeld, Engel, & Herrmann, 2014), memory consolidation (Marshall et al., 2006), fluid intelligence (Santarnecchi et al., 2013), working memory (Jaušovec & Jaušovec, 2014) and motor performance (Brittain et al., 2013; Joundi et al., 2012; Pogosyan et al., 2009). Crucially, these effects are thought to be related to interactions between ongoing brain oscillatory activity and the tACS-imposed oscillatory activity. Combined tACS-EEG approaches have been used in humans to precisely characterize the neurophysiological basis of the abovementioned tACS-induced effects. In particular, the effects of tACS stimulation on EEG rhythms have been investigated. Adopting a 10 Hz tACS protocol, previous reports

demonstrated a specific increment in EEG power spectral density (PSD) in the adjacent (8, 13) Hz band (i.e., α-band) during and after stimulation (Helfrich et al., 2014a). The increase in alpha power was observed at parietal-occipital sites, where the alpha rhythm is typically dominant. Apart from the α-band, a recent review highlighted that at present there is scarce evidence of direct tACS-induced modulation of other brain rhythms (Veniero et al., 2015). Nonetheless, by adopting a 20 Hz tACS frequency protocol over motor cortex, previous studies induced movement slowing (Joundi et al., 2012; Pogosyan et al., 2009; Wach et al., 2013b) and reported modulation of automatic motor inhibition (Cappon, D'Ostilio, et al., 2016). These evidence suggest that 20 Hz tACS stimulation interacts with the dominant EEG rhythm in the human motor system, namely the ß-band (13, 30) Hz. In fact, ß-band synchronization (i.e., increase in PSD) is typically observed during tonic muscular contractions while beta de-synchronization (i.e., decrease in PSD) occurs prior to and during voluntary movements (Pfurtscheller & Lopes da Silva, 1999). Moreover, changes in ß-power are synchronized with simultaneously recorded electromyogram (EMG) activity in contralateral hand muscles (Stuart N Baker, 2007) and aberration of β-bands oscillations are present in movement-related disturbances, such as Parkinson's disease and dystonia (Brown, 2007; Hammond et al., 2007; Kühn et al., 2008). Despite the promising behavioural findings, to date there are no direct EEG evidence for the modulation of sensorimotor β activity after 20 Hz tACS interventions. Hence the underlying neurophysiological mechanisms of 20 Hz tACS are scarcely understood. To fill this gap, the present study employed a combined EEG-tACS approach in order to measure time-varying changes in α and β-bands following tACS stimulation at 10 and 20 Hz. Importantly, we adopted a EEG-tACS co-registration methodology which allowed us to record EEG right after stimulation from a large array of EEG sensors (i.e., 45). Firstly, we tested the hypothesis that 20 Hz tACS over supplementary motor area and

the primary motor cortex (simultaneous tACS of SMA-M1) synchronizes local cortical activity in the ß-band. As a control condition, we also applied a 10Hz tACS on the same area, to verify that the effects on the ß-band were specific for the 20Hz stimulation. We expected the 10 Hz stimulation not to affect ß-band over the motor circuit. Secondly, in line with previous reports, we hypothesized that 10 Hz stimulation would enhance the endogenous alpha oscillations, which are more prominent over parietal-occipital scalp sites.

7.1.2 Materials and Methods

Participants

Eighteen healthy volunteers (10 females, 26–33 years, mean age = 29 year; 2 excluded due to technical difficulties during data acquisition) participated in the experiment. They had no history of neurological, psychiatric, or other medical problems and no contraindications to TMS and tDCS. They also stated that they did not take drugs or alcohol in the days preceding the experiments. Participants were fully informed about the nature of the research and signed an informed consent before starting the experiment. The study was approved by the local ethical committee and was conducted in line with the Declaration of Helsinki.

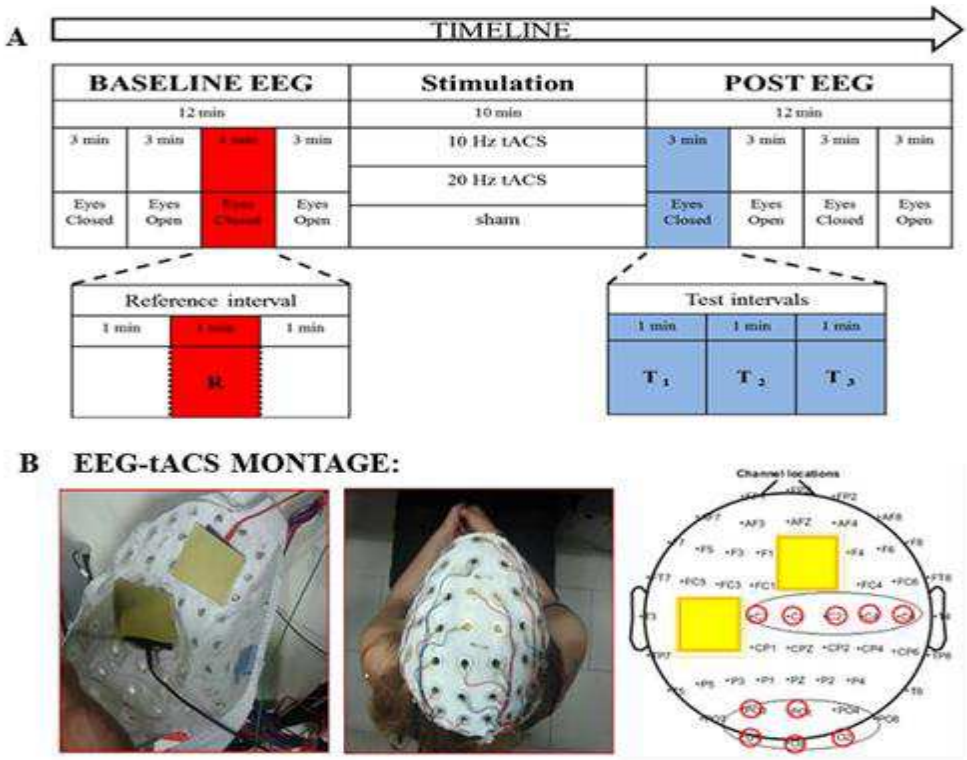


Figure 40: *A: Experimental Procedure. Within subject design, each participant participated in three Sessions (pseudo randomized order) corresponding to the stimulation condition (sham,10Hz,20Hz) in three separate days; B: EEG- tACS Montage;*

General Procedures

Participants were seated comfortably in a chair and were instructed to relax. The experiment consisted in three phases lasting 12, 10 and 12 minutes, respectively (see Figure 40). During the first 12 minutes the EEG was recorded while the subjects were prompted to consecutively keep their eyes closed and opened for three minutes. Immediately after the end of the first phase, either tACS or sham stimulation was delivered for 10 minutes. During this interval participants were asked to fixate a white cross (3×3 cm) in the middle of a black screen and to maintain a relaxed position. Details on stimulations are given in Section 2.3.2. Immediately after the second phase, EEG was recorded again, while the subjects repeated the same eyes closed/eyes opened pattern as in the first phase.

The eyes closed/eyes opened paradigm was utilized to allow further investigations on how tACS determines changes in the reactivity of α-band (see, e.g., Goljahani et al., 2012). However, data taken into account in this first study are those relative to the last eyes closed interval before the stimulation (highlighted in red in Figure 40) and the first eyes closed condition immediately after the stimulation (highlighted in blue in Figure 40).

Data acquisition

EEG recordings

As shown in Figure 40, EEG was recorded from 45 TMS-compatible Ag/AgCl pellet electrodes mounted on a modified 64-channels cap (EasyCap Inc., Herrsching, Germany), according to the 10-20 international system: AF4, AF8, F1, F3, F4, F5, F6, F7, F8, FC1, FC4, FC5, FC6, FP1, FPZ, FT7, FT8, C1, C2 C4, C6, CP1, CP2, CP4, CP6, CPZ, CZ, T4, T5, T6, TP8, P1, P2, P3, P4, P5, PO3, PO4, PO7, PO8, POZ, PZ, O1, O2, OZ. The missing eight electrodes, namely Fz, F2, FCz, FC2, C3, C5, CP5, CP3, were excluded from the montage to make room for tACS electrodes. The electrodes' impedance was kept below 5 kΩ and recordings were referenced online to linked mastoids. Eye movements and eye blinks were monitored by vertical and horizontal electro-oculograms (EOGs), recorded using a bipolar montage. The electrodes pairs were placed at the supra and suborbit of the right eye and at the external canthi of the eyes, respectively. Signals were amplified by a TMS-compatible AC amplifier (Micromed SD MRI, Micromed Srl., Mogliano Veneto, Italy) designed to work in presence of high external magnetic fields as used in TMS or MRI (Morbidi et al., 2007), and sampled at 512 Hz. The amplifier was optically connected to a PC where the software Brain-Quick System Plus was installed. The software was used to monitor the EEG, to manage recording settings and markers, and to store data for offline analysis.

tACS stimulation

tACS was delivered by a battery driven current stimulator (BrainStim, EMS, Bologna, Italy) through surface saline-soaked sponge electrodes (sized 5 × 7 cm), in accordance with current safety limits (Marom Bikson et al., 2016; Michael A. Nitsche et al., 2008; Michael A Nitsche et al., 2003). The sinusoidal stimulation was applied for 10 minutes at an intensity of 1 mA (−0.5/+0.5), with a fade in/out interval of 30 seconds. Two stimulation frequencies were utilized in the experiment, namely, 10 Hz and 20 Hz, yielding, respectively, 6000 cycles and 12000 cycles in each 10 minutes stimulation. Stimulation was delivered by placing one electrode over the left M1 area (FDI hotspot) and the other over the SMA, that is, three cm anterior to CZ, as suggested by our previous study (Cappon, D'Ostilio, et al., 2016). The two spots correspond to the EEG electrodes C3, C5, CP5, CP3 and Fz, F2, FCz, FC2, respectively, and are delimited by yellow squares in Figure 40. The setup was optimized to ensure that impedance, as measured by the stimulation device, was less than 10 kΩ. A sham condition, with no real stimulation, was considered as well, to discriminate between stimulation related changes and other phenomena not related to stimulation. Since a mild itching or tingling sensation under the electrodes was reported during the ramping up phase of the stimulation, in the sham condition tACS was terminated after 30 s in order to make the subject unaware of the absence of stimulation. The three stimulation sessions (sham, 10 Hz, 20 Hz) were tested in a pseudorandomized order across the days. A questionnaire to measure the feelings elicited by stimulation was given at the end of each experimental session (Fertonani et al., 2015) and participants reported that they not perceived or only perceived phosphenes the first few seconds of tACS stimulation in all three stimulation sessions (10Hz, 20Hz, sham).

Data processing

EEG data stored during the experiments were elaborated offline to, first, remove signal components out of the scope of the current investigation and possible artifactual activities not produced by brain sources, and, then, compute the quantities of interest for our investigation. Specifically, recordings were band-pass and notch filtered, with high pass and low pass cut-off frequencies of 1 Hz and 70 Hz, respectively, and notch frequencies centred around 50 Hz. Then, noisy portions of the signal were removed by visual inspection and ocular/muscular components were isolated and subtracted by means of the Independent Component Analysis (ICA) approach provided in EEGLab 13.5.4b (Delorme & Makeig, 2004). For each stimulation condition, that is, 10 Hz, 20 Hz and sham, changes in power spectral densities (PSD) before and after the stimulation were evaluated for two frequency intervals, namely, α-band (8, 13) Hz and β-band (14, 30) Hz. In order to investigate the duration of tACS effect, the eyes closed interval after the stimulation, highlighted in blue in Figure 40, was divided in three consecutive one-minute intervals, denoted as T_1, T_2, and T_3, with T_1 representing the interval closest to the stimulation and T_3 the furthest. Accordingly, for each stimulation condition and band, three power variations were computed by taking as reference the one minute interval in the centre of the eyes closed interval preceding the stimulation (R), and as test intervals T_1, T_2, and T_3. The reader is referred to Figure 40 for a schematic visualization of the reference and test intervals. Power variations were computed by means of the custom analysis support provided by the Channel Reactivity Based (CRB) toolbox for EEGLAB (Goljahani et al., 2012; Goljahani, Bisiacchi, & Sparacino, 2014). Specifically, for each 1 minute reference and test interval, a power spectral density (PSD) was computed by means of the Welch method (Welch, 1967), with 1 second segments and Hanning windowing. The PSD of a signal is a function that shows the distribution of the signal's power among its frequency

components. Red and blue curves reported in Figure 40 are examples of portions of PSDs, computed for reference and test intervals data, respectively. β-band powers in the reference and test intervals, denoted as P^{β}_{ref} and $P^{\beta}_{test,}$ were obtained by computing, for each reference and test PSD, respectively, the areas under the curves in correspondence with the (14, 30) Hz interval. Similarly, α-band powers, denoted as P^{α}_{ref} and $P^{\alpha}_{test,}$ respectively, were obtained by evaluating the areas in correspondence with the (8, 13) Hz interval. Note that for each T_i interval a P_{ref} was computed. Finally, power changes were expressed as percentage relative power variations, accordingly with the event-related synchronization/desynchronization (ERS/ERD) index (Pfurtscheller & Lopes da Silva, 1999). Specifically,

$$\Delta_{power}^{\{\alpha, \beta\}} = (P^{\{\alpha, \beta\}}_{test} - P^{\{\alpha, \beta\}}_{ref}) / P^{\{\alpha, \beta\}}_{ref} \times 100 \qquad (1)$$

where Δ_{power} denotes the percentage relative variation of powers, P_{ref} and P_{test} are the powers in the reference and test intervals, respectively, and the apexes $^{\{\alpha, \beta\}}$ denote either alpha or beta cases. Note that a positive value of Δ_{power} means an increase in power after the stimulation, and a negative one a decrease.

As a further support to our findings a wavelet analysis was performed by using the BRAINSTORM software (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011). Morlet wavelet transformation was applied for each 1 Hz frequency bin between 1 and 60 Hz, using a mother wavelet at 1 Hz with 3 seconds time-resolution (as calculated by the Full Width at Half Maximum; FWHM).

Statistical analysis

For the purpose of statistical analysis, power variations, computed as explained in section 2.4, were averaged over two clusters: one occipital, including O1, Oz, O2, POz, PO3 and

one central, including C1, Cz, C2, C4, and C6. The two clusters are surrounded in Figure 40 by two black ovals. For each cluster (occipital and central), frequency band (alpha and beta) and test interval (T_1, T_2, and T_3) (see Figure 40) the effects of stimulation (10Hz tACS, 20Hz tACS, and sham) on power variations (Δ_{power}) were compared by means of one-way ANOVAs. Variations were tested against the sham condition in order to identify modulations actually due to tACS. Tukey post hoc test were used for significant main effects and interactions.

7.1.3 Results

The analysis described in section 2.5 yielded statically significant results only for variations of β-band power over the central cluster and variations of α-band power over the occipital cluster. Results of the central cluster and occipital cluster are graphically reported, in Figures 41 and 42, respectively.

Central Cluster

As far as the central cluster is concerned, significant effects of stimulation condition were found both at T1 ($F(2, 230) = 8.047$, $p < .01$) and at T2 ($F(2, 230) = 5.935$, $p < .01$) , but not at T3. Post-hoc analysis revealed a significant increase of β power equal to 15% immediately after the 20 Hz stimulation, that is at T1, as shown in Fig. 39. The increase was found to be significantly higher compared to that observed for the sham condition (diff = 14.32 , $p < .01$), which instead was equal to 1.5% on average. Although less pronounced, an increase in β power was observed also at T2 (7% on average) and it was found to be significantly higher than the sham condition (diff = 12.71, $p < .01$). Instead, no significant differences were observed during the third minute after the stimulation. In the same central area, slight increases in β power were observed also in case of 10 Hz stimulation, but they were found to be not significant.

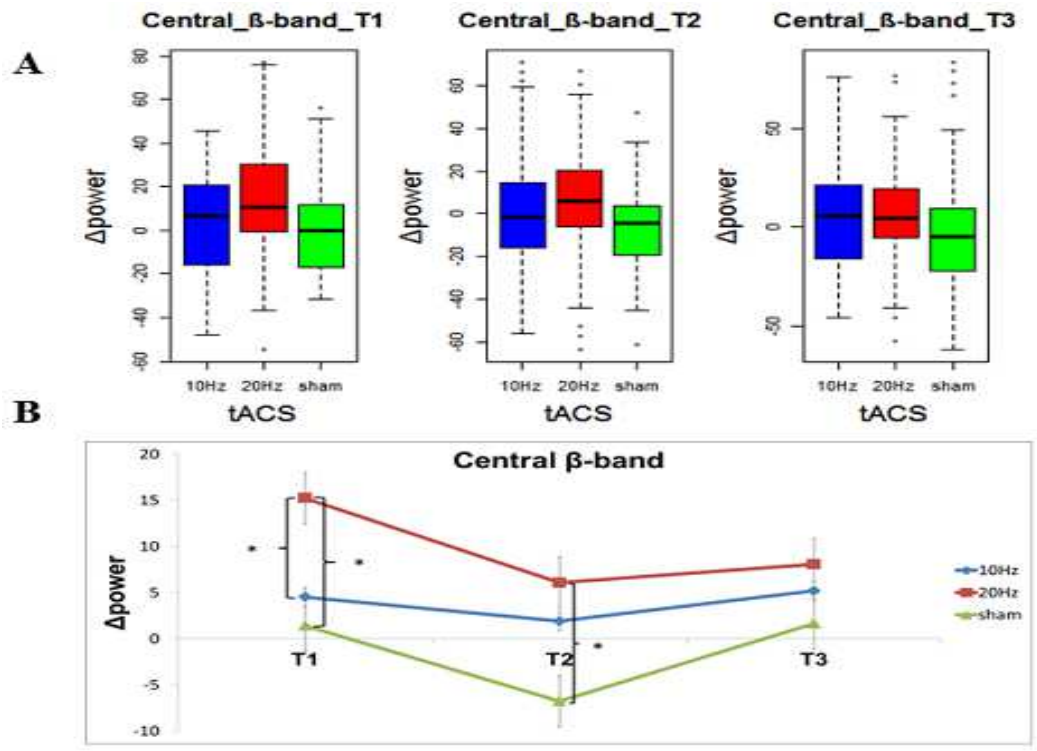


Figure 41: *A: boxplot showing distribution of β-band Δ_{power} values on the central cluster for the three stimulation conditions 10Hz (blue), 20Hz (red) and sham (green); B: average β-band Δ_{power} for the three stimulation conditions 10Hz (blue), 20Hz (red) and sham (green) at the three time points, the first (T_1), the second (T_2) and the third (T_3) minutes after tACS stimulation.*

Occipital Cluster

Similarly, for occipital cluster and α-power variations, there were significant differences between test and reference period both at T1 ($F(2, 230) = 5.085$, $p < .01$) and at T2 ($F(2, 230) = 14.97$, $p < .01$), but not at T3, showing that the effect has a limited duration. Post-hoc analysis, for the factor stimulation revealed that over the occipital cluster the stimulation at 10Hz determined an increase in α-power significantly higher than that observed in the sham condition both at T1 (diff = 26.34 , $p < .01$) and T2 (diff = 43.87, $p < .01$); in the same area, also the stimulation at 20Hz significantly increase the α-band power with respect to the sham condition (diff = 40.75, $p < .01$), but the effect was delayed to T2.

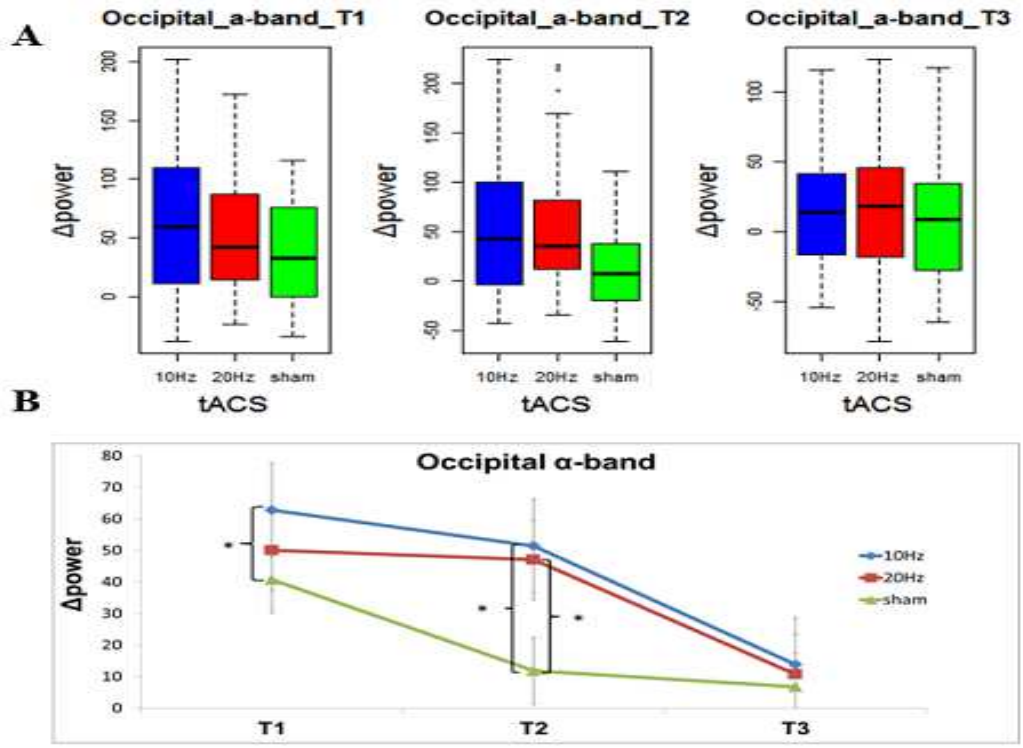


Figure 42: *A: boxplot showing distribution of α-band Δ_{power} values on the occipital cluster for the three stimulation conditions 10Hz (blue), 20Hz (red) and sham (green); B: average α-band Δ_{power} for the three stimulation conditions 10Hz (blue), 20Hz (red) and sham (green) at the three time points, the first (T_1), the second (T_2) and the third (T_3) minutes after tACS stimulation.*

As an illustrative case, Figure 43(B) shows power spectral densities (PSDs) computed with data from the central electrode C4. For each stimulation condition, i.e., 10 Hz, sham, and 20 Hz, PSDs relative to 1 minute before the stimulation (red curve) and 1 minute after the stimulation (blue curve) are drawn in the same plot. As the figure shows, for the 20 Hz stimulation (first plot in the figure) the blue curve is significantly above the red curve for the whole β-band interval (note that the x-axis only includes frequencies from 13 to 30 Hz). The phenomenon of β-band power increase with the 20 Hz stimulation is even more evident in Figure 43(A), where the wavelet representation of data from C4

shows a clear increase in the β range after the 20 Hz respect to the 10 Hz and the sham condition.

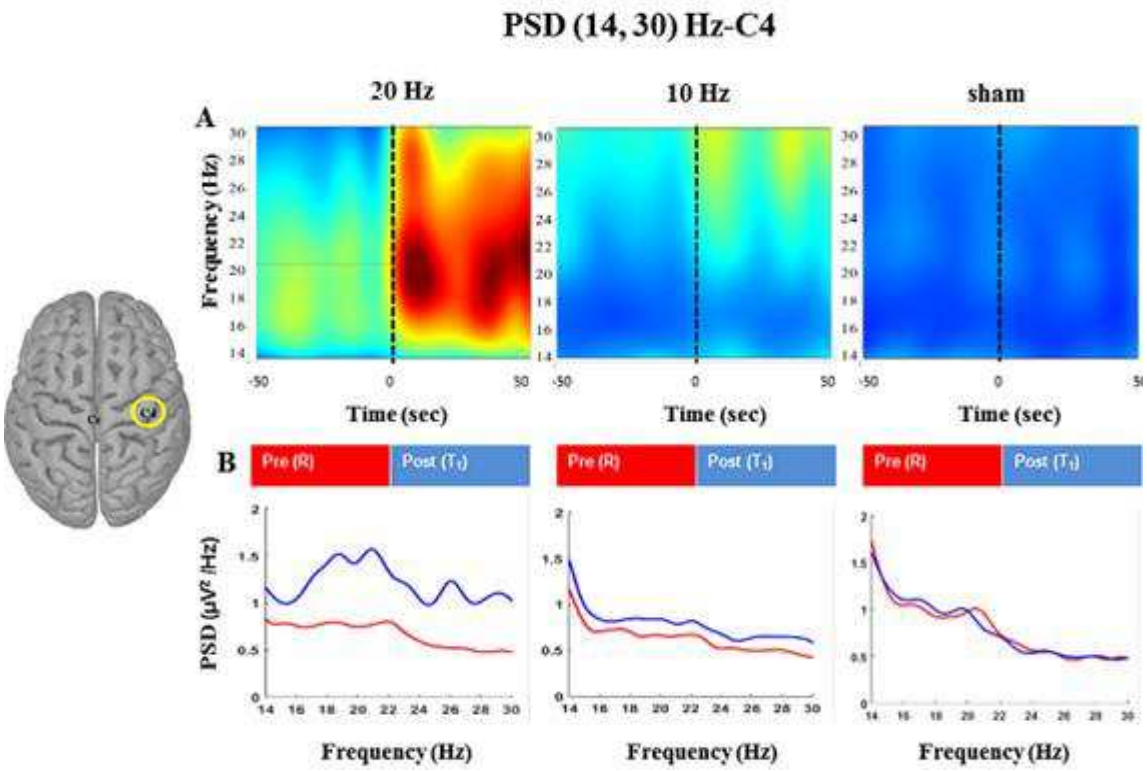


Figure 43*: A: Time-frequency wavelet representations (grand average of all participants) of Δpower values relative to the central electrode C4 for the 20 Hz (left panel), 10 Hz (central panel) and the sham (right panel) tACS conditions. The zeros on the x-axes delimit the intervals before tACS stimulation (leftsides) and the interval after the stimulation (right-sides). B: Power Spectral Densities (PSDs) computed with data from the central representative electrode C4. For each stimulation condition, the PSDs relative to one minute before the stimulation (red curve) and one minute after the stimulation (blu curve) are drawn in the same plot. The frequency range of the plots is limited to the beta (13, 30) Hz.*

7.1.4 Discussion

In an effort to elucidate the efficacy of tACS in modulating specific oscillatory network activity, we performed a combined EEG-tACS study. Here, we measured changes in the power spectral density (PSD) of oscillatory EEG activity during resting state, before and after tACS in two frequency intervals, namely, α-band (8, 13) Hz and β-band (14, 30) Hz. Through recording of EEG activity, we identified β-band oscillations as being

significantly amplified by the application of 20Hz tACS over motor cortical areas. To our knowledge, this is the first study to report a 20 Hz tACS-induced modulation of sensorimotor β rhythm. In addition, in line with previous reports, increases of α-band PSD were observed over the occipital cortex after the 10Hz tACS. Furthermore, our EEG-tACS co-registration methodology allowed us to record EEG right after stimulation from a large array of EEG sensors, drastically increasing the precision of the measurements compared to previous studies.

There is a large volume of electrophysiological evidence describing the presence of β-band oscillations during tonic contractions, its suppression prior to and during voluntary movement (Pfurtscheller & Lopes da Silva, 1999) and its increase during successful response inhibition (N. Swann et al., 2009b). Moreover, it has been reported that 20 Hz tACS stimulation of human motor cortex results in slowed movement (Joundi et al., 2012; Pogosyan et al., 2009; Wach et al., 2013a) and prolonged duration of automatic inhibition in healthy volunteers (Cappon, D'Ostilio, et al., 2016). Those initial studies, while providing valuable behavioural data did not measure the direct impact of tACS on sensorimotor β-band oscillations. Nonetheless, these purely behavioural reports are consistent with our finding that tACS at 20Hz potentiate β-band oscillations in the sensory motor cortex. Crucially, our results provide potential neurophysiological explanation for the observed effects on motor performance. Our results showed that the increase in β-power is maximal during the first seconds after the stimulation, then it decreases and it is no more detectable after 3 minutes both for the stimulation at 10 Hz and 20 Hz. A first possible explanation, considering that our tACS protocol consisted in 6000 (10Hz) and 12000 (20Hz) cycles applied to synchronize the natural oscillations, is that the PSD changes immediately after the stimulation reflected lasting "entrainment" of EEG oscillations adjacent to the stimulation frequency. In their interesting study, Thut et

al. (Thut, Schyns, and Gross 2011, pp. 3) identified four characteristics of the entrainment phenomenon: "*1) Entrainment requires the involvement of a neural oscillator. (2) Entrainment requires periodicity in the input stream of external events. (3) Entrainment requires synchronization (phase alignment) between the input stream and the neural oscillator. (4) Crucially, the models also assume that the external force influences the oscillating elements by direct interaction"*. Although entrainment is by definition an online phenomenon, a previous study demonstrated that it can influence the after effects of tACS (Helfrich et al., 2014a). We propose that a possible explanation for the short duration of the after effects is that we did not lock the external tACS to the ongoing natural frequency in each individual. Thus, longer lasting effects might have been observed if we had been able to phase-lock tACS to the ongoing natural α- and β-frequency in each individual. This concept also extends to entrainment with rhythmic transcranial magnetic stimulation (TMS); accordingly, Romei and colleagues recently demonstrated that entrainment of human motor cortical activity is more evident when the frequency of repetitive TMS matches the individual beta peak frequency (Romei et al., 2016). Another possible explanation for PSD changes after alternating periodic stimulation is that continuous tACS drives short term plastic changes in synaptic organization. According to Hebbian rule, timing is crucial. Indeed, the Spike Timing Dependent Plasticity (STDP) phenomenon highlights that only synapses in which the presynaptic neuron consistently fires slightly before the postsynaptic discharge get stronger, leading to long term potentiation (LTP). LTP can be defined as a long-lasting and activity-dependent increase in synaptic efficacy. Inversely, in long term depression (LTD), the presynaptic neuron fires after the postsynaptic axon leading to a long-lasting and activity-dependent decrease in synaptic efficacy (Mockett, Coussens, & Abraham, 2002). Vossen and colleagues (Vossen, Gross, & Thut, 2014b) proposed a speculative

model based on an intermittent tACS protocol. This model acknowledged the importance of stimulating considering the natural individual alpha frequency (IAF) in order to potentiate the entraining effect taking advantage of STDP principles. Along these lines, online entrainment is the prerequisite into longer-lasting synaptic plasticity effects that translate into frequency-specific changes in oscillatory activity. Importantly, tACS effectiveness is thought to be related to how spontaneous brain oscillatory activity interacts with tACS-imposed oscillatory activity. In fact, we know from previous reports that the activation state of the cortex is likely to influence the tACS effects (Ruhnau et al., 2016). Besides, it has been proposed that slow frequency EEG oscillations may represent the activity of large-scale neuronal networks in the brain, whereas higher-frequency oscillations may reflects the activity of narrower neuronal populations (Singer, 1993). In the current study, we found that tACS caused both local and distant cortical dynamics changes. In particular, we observed significant tACS-induced modulation of β-band specifically over the sensory motor cortex (local). In addition, variations of α-band PSD were observed over the occipital cortex (distant). We proposed that these changes in cortical dynamics reflect an interaction between tACS and the synchronous current changes in local and distant populations of neurons in the cortex. Therefore, the increase of α-band over occipital regions might be explained by the fact that the maximal α-band activity is detectable over occipital electrodes during resting-state conditions, especially with eyes closed. A similar argument was also yield by Rosanova and colleagues (Rosanova et al., 2009) suggesting that each cortical area preserves its own natural frequency when indirectly engaged by TMS through distal brain connections. However it has to be mentioned that a previous study failed to find the same pattern. Ruhnau and colleagues (2016) reported no stimulation-induced entrainment in occipital α during closed eyes resting state (Ruhnau et al., 2016). This inconsistency can be explained by

differences in the experimental paradigms. In Ruhnau and colleagues' experiment participants performed a vigilance detection task during tACS while in our paradigm tACS was delivered when participants were at rest. This was done in order to avoid any potential confound resulting from the summative effects of specific cognitive state and tACS. Indeed, prior studies demonstrated α-band PSD reduction in response to a variety of tasks (Klimesch, 2012). Moreover, Ruhnau et al. applied tACS stimulation over different positions (Cz-Oz Vs SMA-M1) and for a longer time (20 min. Vs 10 min.). In line with our results, an interesting study of Cabral-Calderin and colleagues (Cabral-Calderin, Anne Weinrich, et al., 2016) with a combined tACS and fMRI methodology, applying 10 Hz tACS demonstrated brain metabolism changes in cortical regions far from tACS electrodes (Oz-Cz). Despite the growing interest and findings in the field, at present the underlying mechanisms of how tACS stimulation interacts with the activity of specific neural populations remain unclear. An important attempt to discover the cellular mechanisms underlying the 20 Hz tACS effects came from Guerra and colleagues (Guerra et al., 2016). By combining tACS and TMS the authors identified which cortical inter-neuronal populations respond to 20 Hz tACS applied over motor cortex. Their results indicated that Short Afferent Inhibition (SAI) (Tokimura et al., 2000) was suppressed during 20 Hz tACS. SAI is thought to be related to cholinergic inhibition (Di Lazzaro et al., 2000) and is considered a measure of sensorimotor interaction (Raij et al., 2008). Hence, the authors suggested that increase of cortical β-band PSD may maintain the ongoing sensorimotor or cognitive state by reducing inter-neuronal inhibition. It is plausible to speculate that our results, as well as those reporting slowed motor performance following 20 Hz tACS stimulation, derive from modulation of inter-neuronal inhibition, which impacts on the activation of the motor cortex. Future studies ought to precisely define whether and how these processes take place, for instance through the use

of intracranial recording on specific neuronal populations combined with 20 Hz tACS. Moreover, it would be extremely interesting to analyse EEG data during stimulation, to better characterise the entrainment phenomenon online. Being an electric stimulation, tACS interferes with EEG recording. Although the methodological difficulties, attempts to remove tACS-induced artefact have been made recently (Helfrich et al., 2014a; Neuling et al., 2015; Vossen et al., 2014a). Even so, to measure the tACS after effects EEG had to be recorded offline stimulation in almost all studies (Veniero et al., 2015).

Conclusions

Summarizing, oscillatory rhythms in the brain such as α-band and β-band oscillations contribute to brain activity in a broad sense, ranging from sensory and motor functioning to high-level cognitive processes. We are the first to observed tACS induced changes in β-band in the sensorimotor cortex after the application of 20 Hz tACS. Further, in line with previous reports, we found that α-band oscillations increased in the occipital cortex after the application of 10 Hz tACS, suggesting a frequency and regional specific interaction between specific tACS stimulation frequency and EEG rhythms. Further studies need to explore how the brain respond to tACS, in particular measuring cortical dynamics and connectivity during and after stimulation. In addition, many studies demonstrated that neurological and mental diseases are characterized by aberrant functionality of specific brain oscillations, hence future studies are also important to elucidate the possibility that alternating current might be effective in shaping network dynamics in clinical applications.

8 General Conclusion

The current thesis aims are two-fold: the first is to bridge lines of research on the automatic mechanisms of motor inhibition and on the role of beta oscillation in the sensorimotor system. To investigate this hypothesis I have exploited the ability of transcranial alternating stimulation (tACS) to modulate perceptual and cognitive processes in a frequency specific manner. The second aim was to investigate the neurophysiological mechanisms underlying the effects of tACS applied at physiological relevant beta (20 Hz) and alpha (10 Hz) frequencies on motor cortical neuronal dynamics. Specifically, I adopted combined approach tACS-TMS and tACS-EEG to characterize respectively the modulation of corticospinal excitability and the interactions with the neuronal dynamics. I presented studies that I conducted during my PhD. Chapter 4 presents a review of the literature highlighting the limits, the methodological issues and technical aspects of the tDCS in modulating cognition (electrode position and dimension; current intensity; duration of protocol, inclusion of appropriate assessment tools for cognition, optimal timing for administration of tDCS for cognitive rehabilitation). In chapter 5, I investigate the potential of a new emerging technique - tACS. By a combined TMS-tACS approach I investigated the neuromodulatory effects of tACS on motor corticospinal excitability. Chapter 6 aimed to investigate the functional role of beta frequency in the automatic motor processes. Finally, in chapter 7 I have combined tACS and EEG with the aim to investigate the neuromodulatory effects of tACS on motor cortex neuronal oscillatory dynamics. The findings from these studies provide insight into the understanding and the practical application of transcranial alternating current stimulation in modulating motor neuronal dynamics. Overall, this work contributes to our understanding of the human motor system while offering new insights into the combined

approach of tACS and EEG in the characterization of a causal role of neuronal oscillatory dynamics on behaviour.

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